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Temporal cognition as a feature of working memory

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Contents

Abstract

Psychological studies of the way in which animals time intervals show a key scalar regularity. Namely, the standard deviation of the estimates of the interval length is proportional to the (typically nearly unbiased) mean of the estimates over multiple trials. This implies that the discriminative stimuli for animal behaviour in a timing task are subject to multiplicative noise. Despite a rich body of psychological models of timing, there is a dearth of physiologically-based accounts which explain this regularity.

We propose a theory of interval timing based on the experimentally observed dynamical behaviour of cortical cells during Delayed Match to Sample working memory tasks. These neurons display a diverse array of repeatable temporal activity patterns (collectively termed persistent activity) in the delay period that follows the presentation of a stimulus in each trial. We treat these patterns as forming a temporal basis function representation of the time elapsed since the stimulus was shown. Recent electro-physiological data from parietal cortex, by Shafi, Bodner, Zhou and Fuster (2003) suggest that the standard deviation in the activity of individual cells at a given point in time across trials scales linearly the with mean activity of the cell at that time.

Our model of sustained activity uses the inherent unreliability of synapses within a recurrent network of spiking cells to generate multiplicative noise internally. This mechanism, initially proposed by Shapiro, Wearden and Barone (2003), at all times renders the process of spike generation dependent on the post-stimulus history of synaptic releases. Persistent activity is generated without the need for bistable neurons by the percolation of spikes around the network. Activity levels are controlled by making the average probability that a neuron emits a spike, given that a spike has arrived at a presynaptic terminal, inversely proportional to the neuron's recurrent connectivity. Storage is initiated by a signal which resets the activity to a well defined and reproducible level. It is terminated either by an equivalent signal or as a consequence of the decay of the memory trace.

Time estimates are made via threshold discrimination of the mean activity of the neural population. Random synaptic failures between the cells give rise to the proportional relationship between the standard deviation of the distribution of time estimates and the distribution mean over any set of trials. This makes our proposal consistent with relevant psychological and physiological results.

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Finally I could not have written this thesis without the kindness and warm heart of my girlfriend, Kelly.

Introducing temporal cognition as a feature of working memory

This thesis is concerned with temporal perception. Temporal perception allows animals and humans to keep track of the passage of short time intervals. Here the focus will be on time intervals from about 500 ms to several minutes, a range of four orders of magnitude. Within these limits biological timing is subject to scalar variability. Scalar variability, so intervals that are twice as long are corrupted by twice as much noise.

The proposal of this thesis is that within this range, temporal cognition is an intimate feature of the neural processes which provide a substrate for working memory. Evidence for this comes from diverse sources: psychophysical experiments, single cell electrophysiological studies, accepted theories of temporal perception, behavioural learning and the mechanisms underlying observed neural firing patterns.

In the course of these five chapters a simple neural model of these two faculties will be introduced. This model builds on previous work both in the field of temporal cognition and on the neurophysiology of working memory. This will allow the model to be expounded alongside the data, which inspired it, and which it seeks to explain.

Physiological and psychological data places strong constraints on plausible models of timing. The scalar variability of the perception of different time intervals forms the primary constraint. The scalar property and associated Weber's Law are ubiquitous across interval timing data from a range of experimental tasks and subject species. This forces models which seek to explain psychological timing accurately to include some form of multiplicative noise in the mechanism they use to generate timing traces. This common feature suggests there is some degree of similarity in the dynamics of interval timers from species to species. This issue is addressed in chapter 1.

That physiology has failed to pin-point a discrete area of the brain for which timing is a primary function, also bounds the possible theories of temporal cognition. Few processes so far discovered in the mammalian brain have the enduring periodicities or time-scales required to measure time intervals in the given range. This leaves a theorist with the choice of proposing an as yet undiscovered neural process which has the necessary characteristics or borrowing a neural system already suggested as doing something else, and showing how it can combine timing with its other functional purposes.

This thesis takes the latter approach. The theory outlined in subsequent chapters 'piggy-backs' the timing process on the cognitive function of working memory. This is a short-term store of salient information required for tasks which are to be completed in the near future. Neural activity correlated with this faculty has a relatively long time-scale. It can be rapidly activated and deactivated by relevant external stimuli. Moreover, lesions of the prefrontal cortex (PFC), an anatomical region heavily involved in supporting working memory, result in problems in temporal perception. The characteristics of memory related sustained activity in PFC are discussed in chapter 2.

A critical issue in temporal cognition is how the information collected and measured by internal timers is used by animals to make decisions and eventually take actions. Information about the duration of intervals is only useful if it is combined with goal related information about the value of particular actions to the animal.

Since it is known that, under experimental conditions. the perceived passage of time varies from trial to trial with a scalar variance how can animals make temporal predictions? It is clear that they can make such predictions but are current theories of optimal policy selection able to take into account the variability of animals internal timing cues? These questions are addressed in chapter 3.

Models linking timing and working memory are thus constrained by psychological and physiological evidence. A reduction in the space of reasonable mechanisms and substrates for a model can be a bonus for the theorist. By ruling out intuitively more obvious approaches to a problem, data constraints help point the light of enquiry at theories which attempt to explain features of the data across several experimental levels.

Recurrent networks can be used to integrate inputs, an essential component in the generation of sustained activity in PFC. By modeling the effect of noisy synapses in networks of pyramidal neurons in PFC, the theory proposed in this thesis shows how working memory functions could provide a substrate for time measurements. Chapter 4 brings together evidence from the previous chapters to build a model of temporal estimation based on sustained prefrontal activity.

An example of such an approach is that taken by Wearden and Shapiro who showed that scalar variability can be derived from the unreliability of synapses. Because synapses only effectively transmit an incident spike on less than half the occasions they arrive at the presynaptic bouton they can generate noise which multiplies in a recurrent network.

Having defined a plausible timing mechanism and the functional roles

such a mechanism could be called upon to play, the final part of this thesis will conclude by looking at the means by which the information supplied by an internal cue can be used. Of particular interest are timing disorders which can arise either though malfunction of the timing cue or the read-out mechanism used to draw temporal estimates. Chapter 5 looks at the problems suffered by Parkinson's patients when attempting to estimate time intervals, and possible causes for these deficits within the model previously described.

Chapter 1

Temporal perception

1.1 The characteristics of temporal perception

The passage of time is marked by external events in all sensory modalities. Such events are communicated by visual, auditory or somatosensory signals. Signals which provide predictive cues of later salient events.

A priori it is not clear that these cues are needed to perceive time. One might imagine animals relying on a perpetual internal signal log the order of events and judge the intervals between cause and effect.

However experimental evidence strongly suggests that external cues have a very strong impact on the way in which the passage of time is perceived, at least over short intervals. Moreover the internal timer does not provide a consistent signal from which time intervals may be consistently judged accurately.

Both animals and humans find estimating intervals exactly a hard task. Averaging responses over many trials of an interval timing experiment shows that animal subjects become progressively more uncertain about the interval being timed as that interval extends. Nevertheless subjects demonstrate that they are timing in an unbiased fashion since the average estimated interval is invariably equal to the desired task interval.

Anecdotal evidence suggests that fixed durations seem to pass more rapidly at higher levels of arousal. Several studies have shown that pharmacological agents which induce changes in arousal can shift the mean perceived length of a given interval away from the real time value of the interval. Similar results have been found in psychophysical studies with patients suffering from Parkinson's disease [25]. These subjects lack the normal number of dopaminergic cells in the mid-brains. One effect of dopamine depletion

after training at normal levels of dopamine is that time intervals are subjectively estimated as being longer on average than the interval the subject observed.

The neural mechanism which underlies such perceptual abilities must be far from trivial. It is constrained by data from behavioural experiments with both humans and animals which show that perceived time becomes increasingly variable as the duration of a given real time interval increases. This property allows us to draw parallels between the way in which durations are perceived and other sensory percepts such as the sense of touch which show the same scalar regularity known as Weber's law.

There is little or no evidence for a dedicated region of the brain devoted to event timing. This raises the possibility that the process by which timing occurs might be distributed across the brain. Whether localised or distributed, there is no physiological evidence for long-term rhythmic processes of an appropriate time scale to produce a regular signal of pulses. Because of this we need to look for other regular processes which might provide an internal timing cue while being modulated by external events.

1.1.1 The increasing inaccuracy of estimates: Weber's law applied to timing

The singular feature of short interval timing is that organisms' estimates of any given time period become increasingly inaccurate as the length of that period increases.

Psychophysical measurements in other areas of perception show a similar scalar regularity. Weber, in formulating the law which takes his name, was concerned with the sense of touch [60]. In his experiments he presented two weights for his subjects to hold. On each presentation he asked his subjects which weight was heavier. For any given weight he selected partner weights with the aim of finding the greatest difference in weight which could not be accurately perceived by the subject.

In practice this means that the subject is equally likely to report one of the pair of weights as the heaviest as the other. Weber's discovery was that the weight difference at which two weights no can no longer be accurately differentiated is proportional to the ratio of the two weights being compared. Heavier weights were harder to differentiate.

> When noting a difference between things that have been compared, we do not perceive the difference between the things, but the ratio of the difference to their magnitude.

A further step, Fechner's law, integrates Weber's law to show that the perceived intensity of a stimulus is proportional to logarithm of the true stimulus intensity.

Weber's law applies fully to interval timing. The standard deviation of an animal's estimates of a interval σ_t increases linearly with the length of the interval t. This is seen in every temporal perception study involving short intervals, regardless of the precise details of the procedure.

$$\sigma_t \propto t \tag{1.1}$$

Interestingly this rules out one of the simplest models of event timing. In this model a pacemaker with a fixed underlying rate feeds an accumulator. Noise in this model can arise due to the random variations in the inter-pulse interval of the accumulator. However this noise is non-scalar. The variance of time interval estimates scales with the mean, rather than the standard deviation. This can be remedied by randomly choosing the clock speed from trial to trial.

Killeen, Fetterman and Bizo [6] showed that the psychometric function, describing the probability of responding to the long duration, in a temporal bisection experiment (described in more detail in the next section) could be modeled by a logistic distribution over perceived time.

$$P(r_L) = \left[1 + \exp\left(\frac{T_{1/2} - t}{\frac{\sqrt{3}}{\pi}\sigma_t}\right)\right]^{-1} \tag{1.2}$$

$T_1/2$ is the bisection point and decision criterion.

$$\sigma_t = \sqrt{(\gamma t)^2 + pt + c^2} \tag{1.3}$$

The model has provision for scalar γ, non-scalar p and constant c noise processes. Equation 1.1 describes the same phenomena as the scalar noise term in this model. A pacemaker-accumulator model has non zero p and $\gamma = 0$.

The best way to see that Weber's law holds for data taken in laboratory experiments is to take a graphical approach. The distributions of time measurements made by a subject estimating several different intervals over many trials are re-scaled as follows. Firstly, the distributions of response rate are divided by the maximum response rate. The response data might be the distribution of estimates of a given time, in an interval timing task, or the rate of lever presses for a given delay to reward, in a peak procedure experiment. Secondly, the measured times for each response distribution are

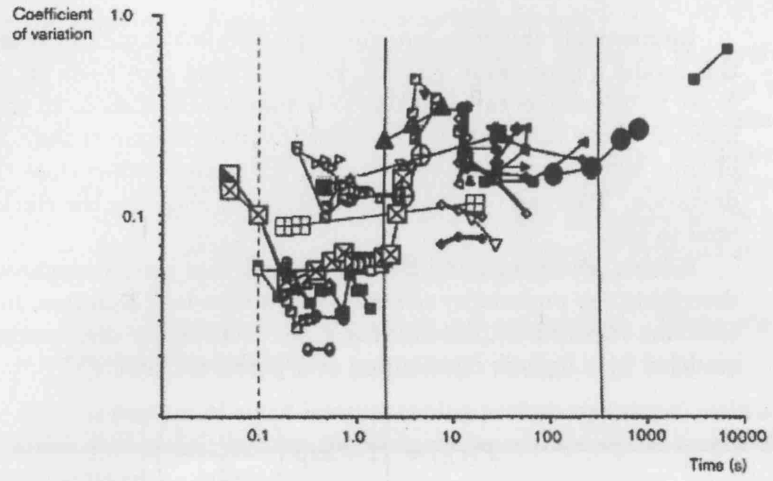

Figure 1.1: Data from a number of human and animal timing studies point to Weber scaling. Here the coefficient of variation is plotted against the interval time being estimated for a number of human and animal studies. The range of time intervals over which the Weber Law holds is remarkable. Note that both axes are on a logarithmic scale [25].

divided by the time at which the peak response occurred. The peak of each distribution should now be at co-ordinates (1,1) on the plot. One should also see that, for individual subjects, the estimate distributions for different time intervals overlap. Examples of this can be seen in both human and animal data in figure 1.3 and figure 1.5.

Alternatively consider $\{t^*\}_{t_i}$ a set of estimates of a fixed time t_i. These estimates have a measured standard deviation σ_{t_i}. In normalised coordinates the standard deviation of each estimate distribution is re-scaled as a fraction of the interval being estimated. The standard deviation of distributions in the normalised co-ordinates is the coefficient of variation of the original distributions. If the original distribution of estimates obeys Weber's law (equation 1.1) its coefficient of variation is invariant under different values of t_i.

We know that the estimates which make up the original distributions can be driven by a single underlying process described by a fixed γ and negligible non-scalar p or constant noise c for all t_i.

$$\sigma' = \frac{\sigma_{t_i}}{t_i} = \gamma$$

If a Poisson-like process underlies perceptual timing then we would expect to see that the distributions of estimates of longer intervals would be narrower than the distributions of estimates of shorter intervals in re-scaled space. This is because for a Poisson process $\gamma = 0$ and $\sigma' = \sqrt{\frac{p}{t}}$. As a result the invariance of intervals is lost. Note that Weber's law is not the only important property of timing that we can deduce from these overlapping distributions. We see that the amount of constant noise, known as bias, is insignificant. This means that all significant noise in the timing process comes from the γ term.

It is perhaps not intuitive that perception of time should be invariant in this way. Indeed it may seem odd to suggest, as Weber's law does, that we perceive the difference between a four second and five second duration as easily as we perceive the difference between periods of 16 and 20 seconds. However experiments strongly show that this is the case for event timing and many other perceptual thresholds including the comparison of line length by vision and tone frequency by audition.

Weber's law holds from the lower limits of temporal perception at around 50 milliseconds to around 500 milliseconds [6].

1.1.2 Pharmacological effects on subjective time and arousal

When asked to reproduce a duration in an interval timing task, patients with Parkinson's disease appear to time in a manner which is biased. That is to say they consistently over, or under estimate the interval required. Such patients are observed to produce a distribution of estimates which has a mean which over or under shoots the time which the patient has been asked to reproduce, shown in figure 1.2. Distributions of estimates of different interval durations overlap when re-scaled by peak height and position. However two time scales are no longer perceptually invariant to the patient because there is a non linear bias in the perceptual mechanism.

Parkinson's patients suffer from a gradual death of dopaminergic neurons in the ventral tegmental area, VTA. These cells are not replaced. Cognitive defects associated with the disease are thought to stem from a reduction of the dopamine signal. Dopamine is a neuromodulator which is produced in substantia niagra and transported widely across cortex.

Performance in Interval Timing experiments both on and off a synthetic dopamine replacement drug L-Dopa shows that patients tend to build up biases in their internal timing process when their dopamine level is low. These biases observed at low dopamine levels are non linear because they depend on the sequence in which the patient was trained to reproduce intervals in the experiment [39].

A Parkinsonian without serious cognitive defects will produce results in timing tasks which are indistinguishable from those of control subjects if trained and tested on the Interval Timing task while on L-Dopa medication. Thus the role of dopamine, or its equivalents, in accurate temporal perception is considerable.

L-Dopa is medication is not the only way of restoring temporal cognition in Parkinson's patients. Evidence has been found that stimulation of thalamic pathways through the basal ganglia can also compensate for dopaminergic timing defects in some patients [34].

1.2 Psychological theories of timing: SET, BeT and MTS

Before we proceed much further it is necessary to look at the three psychological theories of interval timing. Much of the experimental work described in the final section of this chapter seeks to build a base of evidence for a psychological theory of timing. The theories are also important as a con-

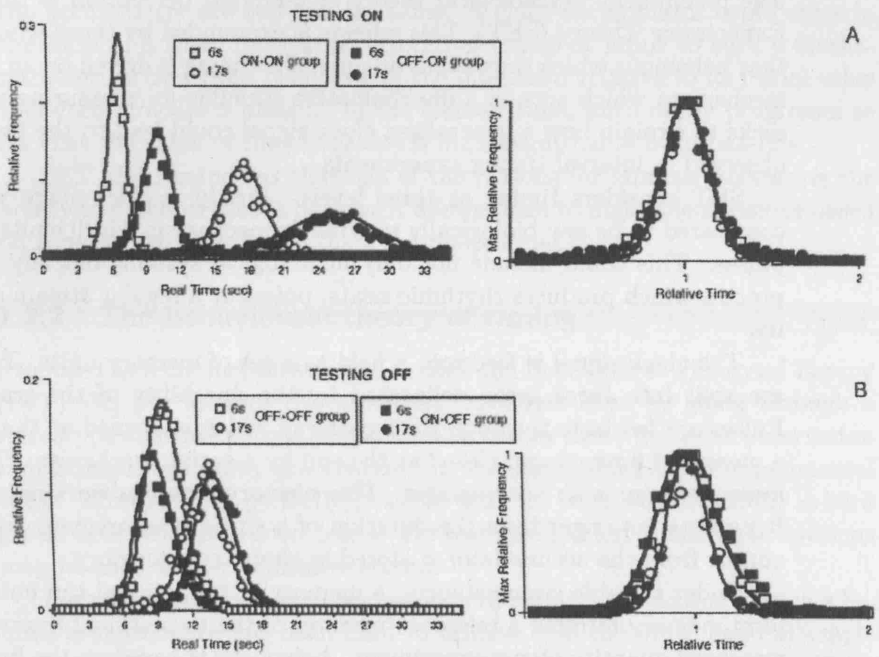

Figure 1.2: Data from Interval Timing experiments with Parkinson's patients. Subjects were split into four groups delineated by their medication state during training or testing. On refers to patients on L-Dopa; off refers to patients without their normal L-Dopa medication. A shows that individuals tested on L-Dopa but trained off are biased to respond long compared with their peers tested on medication. B shows that when tested off medication both those trained on L-Dopa and those trained off tend to migrate toward some intermediate interval.

ceptual framework for describing the process of timing whether or not they provide a complete and accurate explanation of temporal perception.

1.2.1 Scalar expectancy theory

The preeminent psychological theory of temporal perception is the Scalar Expectancy Theory (SET). This scheme is expounded by those who believe that behaviour which shows that an animal is timing is driven by an internal mechanism which acts as a discriminative stimulus for measuring time. It seeks to explain how a generalised clock signal could lead to the behaviour observed in interval timing experiments.

SET considers timing at three levels. Firstly, a clock stage which is considered to be any biologically reasonable mechanism which emits regular pulses. This could include not only neurological systems but any internal process which produces rhythmic beats, pulses or a regular stream of activity.

The clock signal is feed into a held as a set of memory units. The units are split into three areas delineated by the durability of the trace held. Pulses are fed in to memory via a pathway which is opened at the start of a measured interval and closed at the end by a gating mechanism. The first memory stage is an accumulator. This memory acts like working memory. It persists no longer than the duration of a single measurement trial. The output from the accumulator is stored in short term memory.

Under suitable circumstances, a memory of the interval can enter long-term memory forming a reference memory of the to-be-timed interval. The measured quantity of any experiment - behaviour is based on the final decision stage. Here short-term and long-term memory traces are compared to determine the correct action in response to the interval measured.

An immediate objection to SET is its generality. The theory is at the highest possible level far away from the neurological mechanisms which underly the interval timing process.

It fails to provide an account of the scaling phenomena presented in the previous section. In theory any of the components of SET could introduce multiplicative noise into the discriminative signal for time. For instance Weber's law might come to hold due to noise in storage or retrieval of memory traces. However the most frequent assumption is that scalar variability arises because the clock rate varies from trial to trial. One can then consider the pulse rate to be a normally distributed random variable. Several writers have found this arbitrary scheme unsatisfactory. Staddon and Higa's criticisms of SET [58] lead them to propose an alternative, the Multiple

Time-Scale theory.

However SET does provide a reasonable basis upon which to start thinking about the neural mechanisms underlying timing. This is if we do not worry too much about the precise boundaries laid down by the psychological model. For example, one might imagine a situation in which the clock and the accumulator are one and the same. A clock-accumulator could come in the form of a leaky integrator. An initial transient input to such a mechanism decays over time. The level of the integrator relative to its initial value therefore provides a measure of the elapsed time, until decay progresses so far that the value of the integrator is indistinguishable from baseline.

SET also reminds us that one of the reasons for animals possessing the ability to perceive time is because it allows them to make the decisions based on time information where there are no external cues.

1.2.2 The behavioural theory of timing

Proposed as a distinct alternative to SET the Behavioural Theory of Timing (BeT) [32] put forward the idea that organisms time by going through a stereotypical sequence of behaviour. The theory arose from the observation that animals are rarely inactive during the delays inherent in experimental trials. However it is perfectly possible that the sequence of actions is hard for an external observer to detect. For instance a chain of muscle activations may be used as discriminative stimuli.

Perhaps unsurprisingly, concrete experimental confirmation of such a behavioural sequence has been hard to achieve. On the other hand attempts to place BeT on a more mathematical footing have had more success. These ideas centre around a chain of states, rather than behaviours, through which a subject transitions relatively slowly during a timed interval via a Poisson process. This might be thought of analogously to an unstable nuclei decaying through a series of configurations toward stability. At each step the time constant of the process is well defined. This is what accounts for the incredible accuracy of atomic clocks despite their reliance on an underlying system which is inherently probabilistic.

One problem with these ideas is that they presuppose a dedicated architecture for timing; another is that they ignore the issue of how the relationship between the internal timing signal and behaviour is learnt. Weber scaling is explained by BeT by allowing the rate at which the model advances from state to state depends on the inter-reinforcement interval. Specifically the average time between state transitions τ is a linear function of the inter-reinforcement interval T. The probability that the number of states between

the start of an interval and a time t is n is given by $p(N(t) = n)$.

$$p(N(t) = n) = \frac{(t/\tau)^n e^{(-t/\tau)}}{n!}\tau = kT \tag{1.4}$$
$$\tau = kT$$

This gives rise to the scalar properties of timing but predicts that the inter-reinforcement interval should affect temporal perception. This has been shown experimentally not to be the case [4].

1.2.3 Multiple-timescale theory

Dissatisfied with SET's inability to pinpoint a source of scalar variability in temporal perception Staddon and Higa [58] produced a thoughtful albeit much criticised [11, 23, 24, 30] critique of SET which went on to propose an alternative model based on a cascade of leaky integrators each with a incremental increase in time scale.

Central to MTS is the idea from optimal foraging theory that subjective time is measured logarithmically. It is often pointed out that this conclusion is inconsistent with data from time left experiments [24]. However MTS is worth studying despite its failings because it is one of the few theories to attempt to pull together data from ecological and conditioning experiments. The theory attempts to eliminate the concept of a pacemaker from timing. The reason this is undesirable, in the eyes of the the MTS theory, is because such devices, like constant rate Poisson processes, are not subject to scalar variability.

Instead MTS uses a set a of decaying memory traces of stimuli $V^0_{out} = X(t)$ received over the course of a time period such as rewards. The signals from these stimuli are fed into the fastest decaying leaky integrator of a cascade of such integrators which obey the following dynamical equations.

$$V^{(n)}_{out}(t) = \Theta^{(n)}\left(V^{(n-1)}_{out}(t) - V^{(}n)_{in}(t)\right) \tag{1.5}$$
$$\Theta^{(n)}(x) = x, x > \theta^{(n)}$$
$$\Theta^{(n)} = 0, x < \theta^{(n)}$$
$$V^{(n)}_{in}(t+1) = a^{(n)}V^{(n)}_{in}(t) + b^{(n)}V^{(n-1)}(t) \tag{1.6}$$
$$0 < a^{(n)} < 1, b^{(n)} > 0$$
$$a^{(n)} = 1 - \exp(-\lambda n)\lambda > 0$$

There are two dynamic components in each integrator a decay term and a habituation term parameterised by $a^{(n)}$ and $b^{(n)}$ respectively 1.6. The habituation term adjusts the timer depending on the stimulus history. A high stimulus rate will cause the cascade to be driven quickly.

An immediate problem with MTS is that for the estimation of long time intervals it requires a sparse preceeding stimulus history and integrators which leak slowly over the same time scale as the to be measured interval. There is no immediately convincing evidence that such integrators exist in the brain.

1.3 Measuring perceived time: interval timing, temporal bisection, peak procedure and leave time

What experimental tools are available to determine the processes through which time is subjectively perceived? Three common paradigms are Interval Timing, Peak Interval, Temporal Bisection and Leave Time. Each relies on a different action or set of actions being undertaken by the subject at times during the course of an experimental trial. The pattern of behaviour in the absence of external temporal cues allows the existence and properties of an internal time cue to be elucidated. It is important to realise that observations in these experiments are behavioural. This is the source of controversy. One point of view holds that the sequence of behaviour demonstrated by the subject during each experimental trial drives temporal perception. The opposing view proposes that behaviour is controlled by internal timing process initiated by external stimuli. This debate will be discussed in more detail later in this chapter. Before that, what are the experimental approaches to the psychology of timing? Can the phenomena seen in these experiments shed light on the neural mechanisms underling event timing.

1.3.1 Interval timing

Interval Timing is an experimental paradigm typically used with human subjects. To abstract a standard procedure [10] interval timing experiments seek to make is as follows. Albeit true that interval timing experiments rarely follow this procedure for practical reasons. The subject is presented with a start signal which is either a visual or auditory stimulus. At some point after this stimulus he or she is required to press a button indicating the end of some fixed interval, normally a duration of several seconds. Feedback is provided on some or all of the trials indicating to the subject whether the

interval they estimated was longer or shorter than that required. During the trial, an unrelated distractor task may have to be performed, such as memorising a short list of words for recall or reading numbers presented to the subject in pseudo random order at variable intervals. This prevents subjects from counting or using other internal vocalisations as a cue for the task.

Figure 1.3 shows the distribution of time interval reproductions made by a subject in a set of Interval Timing tasks on regular axes and on axes which have been re-scaled to peak height and position respectively. Two intervals, 8 and 21 seconds, are tested separately.

Interval Timing is often used as part of a battery of tests when analysing the cognitive performance of patients. Patient studies have been undertaken [42], using this task, to determine the effects of drugs of abuse and neurological impairments, such as Parkinson's disease and attention deficit disorder on the perception of time.

1.3.2 Temporal bisection

This experimental method introduces subjects to two bounding temporal referents, one short, the other long. These may be presented at the start of each trial on a trial by trial basis, or subjects may experience the referents prior to a set of trials requiring them to remember the duration of the referents throughout a set of trials. The referents are associated with different behavioural responses. On each trial subjects are presented with a probe interval. They must then decide whether the duration of the probe interval is closer to the long or short interval.

These experiments yield a psychometric function, shown in figure 1.4, relating the probability of a long response to a given probe duration. The bisection point is the probe time for which a subject is equally likely to respond long or short. This is the probe interval which the subject finds hardest to classify.

An important issue is whether subjects undertaking these tasks compare the probe interval to memories of the referent intervals or to a criterion duration determined by the observed referent intervals. This threshold interval corresponds to the bisection point. Experimental evidence strongly favours the latter a conceptually simpler option [1]. Subjects tend to ignore referents presented on individual trials in favour of a comparison based on the distribution of all referents observed over the history of trials.

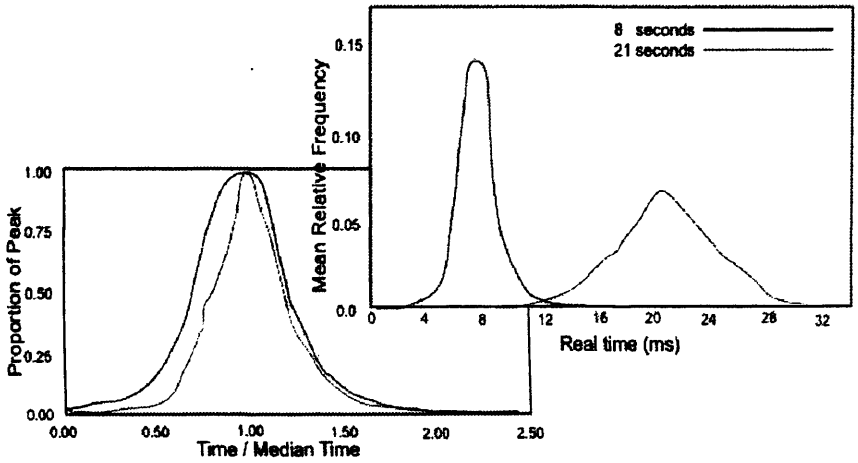

Figure 1.3: Re-scaled and raw data from human interval timing. The uppermost plot shows the distributions of time interval reproductions made by humans asked to time either 8 or 21s while completing a distractor task to prevent them from counting seconds. In the lower plot each data point has been re-scaled to interval and peak-height invariant coordinates. Each point is now plotted as a proportion of the distribution peak to which it belongs and the proportion of the to-be-time interval represented by each estimate. After re-scaling the two distributions overlap. This implies that the standard deviation of each distribution scales with its mean [25].

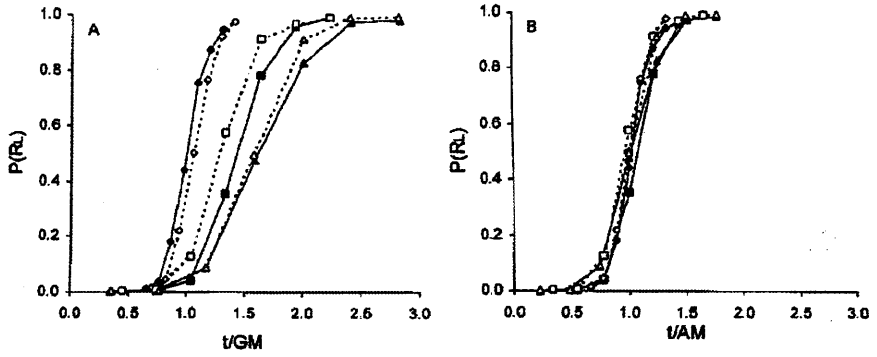

Figure 1.4: Probability of responding long in a temporal bisection task averaged over observers, as a function of time divided by the geometric mean (A) and arithmetic mean (B) of the two referents presented on the trial in question. The ratios of the long to short referent time are indicated by shape (diamonds = 2; squares = 5; triangles = 8).

1.3.3 Peak Interval

Animals cannot be made to perform an Interval Timing task in the standard form described previously. This is because of the difficulty of training animals to make a single unambiguous delayed response to a stimulus. There is also the problem of how to motivate the animal through rewards. Within what time window around the correct response time should a response be rewarded? Too narrow a window and the rate of reward might be too low for the animal to ever learn the task, too wide and the concept of estimating a single distinct interval becomes blurred.

Instead, the effects of cognitive timing are observed in animals' behaviour in experimental paradigms in which the subject is presented with a less abstract goal. Such a goal assumes animals seek food rewards and more importantly seek to maximise the rate at which they receive such rewards.

In a Peak Interval task, like interval timing experiments, the initial stimulus may be either visual or auditory. This stimulus signals that at some precise time after the stimulus onset a food or juice reward will become available if a lever is depressed at that time by the animal undergoing the experiment. In other words a lever press at a fixed interval after the stimulus onset will lead to the delivery of a reward.

The animal has previously been conditioned that lever presses can deliver

a reward so is motivated to press the lever. The initial stimulus remains on throughout the trial until the reward is delivered. This does not provide the animal with any further temporal information during the delay. However unlike a transient stimulus it does not require the animal to remember that the stimulus occurred some time in the past. As learning progresses animals will continue to press the lever throughout the trial while the conditioned stimulus is present.

Partial reinforcement, the practise of randomly rewarding correct behaviour on certain trials means that on some trials the conditioned stimulus is not reinforced. Averaging over un-reinforced trials a characteristic pattern of pressing emerges for each animal over a time course which is longer than the delay interval. These patterns scale with the length of the delay. Typically the average rate of pressing actions in each pattern will increase after the initial stimulus on-set, reaching a peak near the time at which the reward would be delivered in a reinforced trial. Data from pigeons performing this task can be seen in figure 1.5.

Gaps in the conditioned stimulus

One way of carrying out the peak interval experimental paradigm is to present a conditioned stimulus, which remains on for the duration of the fixed interval, prior to the delivery of the reward. In order to dissociate the effect of learning on timing behaviour a type of probe trial is introduced called a gap trial. In these trials the stimulus is switched off for a duration within the interval before resuming prior to the end of the trial.

In experiments with pigeons [14], two distinct effects of the pause were seen. Trials with short gaps saw the peak time to move back by a time slightly longer than that of the gap. When the gap duration moved above some threshold the peak time shifted more dramatically, by a duration slightly less than that of the gap plus the interval prior to it. More recently experiments using both rats and pigeons in a similar paradigm [9] showed that there is a continuum of outcomes between these two shifts. This suggests that during the gap some decay mechanism is at work rolling back the measurement so far made in the trial. If the gap is long enough the timer is effectively reset by the decay.

The complexity of this result is demonstrated by the observation that shorter breaks only lead to a partial reduction in the time estimate. This begs the question as to whether the timer itself produces this complex behaviour or the timer control (setting and resetting) is complex.

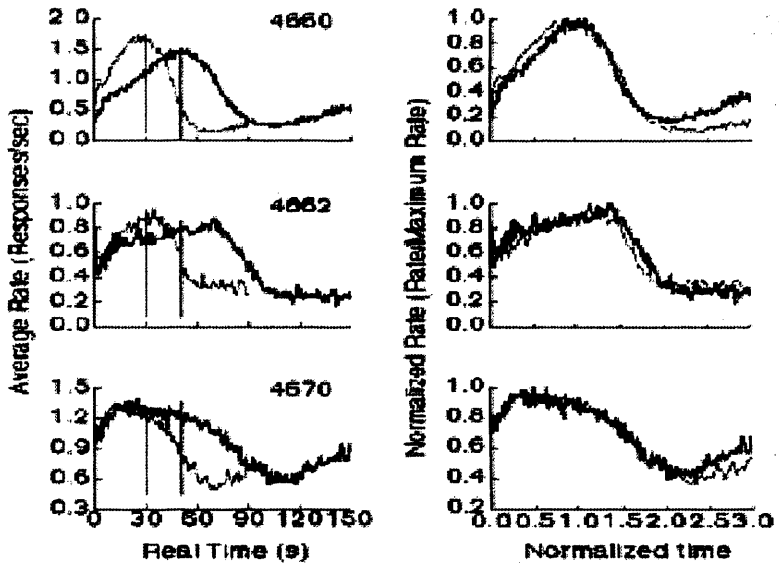

Figure 1.5: Pigeons undertaking a peak procedure task The left hand figures show the average rate of key pecking of three pigeons on the probe trials of two peak procedure tasks. In one task the pigeons have been trained that a reward will be delivered if a key is pecked 30 seconds after trial onset; in the other the interval is 60 seconds. The right hand figures show the same data re-scaled as described in the caption of figure 1.3. It can be seen that the response profiles once more overlap.

Time left

Another variation of the peak interval paradigm allows the experimenter ask the subject to estimate how much time is left in the trial. In this experiment an animal is trained that a signal of one type predicts food will be delivered when a lever is pressed a given interval after the appearance of the signal.

A second, distinctly different, signal predicts food will be delivered if a different lever is pressed. The interval between this signal and delivery of the food is only half as long as the interval linked to the first signal.

The experiment proceeds as follows. At some time in the trial interval after the long-interval stimulus is presented the short-interval stimulus is presented. This indicates to the animal that both levers are primed. The animal therefore has a choice.

Assuming the animal wishes to maximise its rate of income, it needs to chose the action with the shortest latency to reward. This means when the second, short-interval stimulus appears it needs to press the lever which will deliver a reward soonest. If the trial is more than half-way through the reward will be delivered first on the long-interval lever. However if the trial has yet to reach the half way point when the second stimulus appears the reward will be delivered more rapidly if the short-interval lever is pressed.

The decision requires that the learnt duration associated with the short stimulus be compared with the expected duration of the long stimulus and the subjective time which has elapsed since the start of the trial. Here left-time experiments differ from peak interval experiments which do not require time to be tracked during the delay. This has important implications for models which need to be able to provide animals with a time estimate at any point during the trial not simply a cue as to when a learnt interval has elapsed.

1.3.4 Leave time

Other experimenters have looked at another aspect of interval timing, how long an animal is prepared to wait for a reward. The experiments are intimately related to optimal foraging theory [31]. Consider an animal exploiting a patch in which food items arrive with fixed intervals. At some point the patch becomes depleted and food is no longer available. There are no visual or auditory clues that this event has occurred, so the animal is forced to use internal timing to determine when to leave the patch and explore other sites for food. If the animal has learnt to expect reward on a regular schedule it has the information that the patch is depleted after a single un-

rewarded interval of the learnt duration has passed. For optimal foraging the point at which it leaves after the last presentation of food provides a measure of its subjective time estimate of the inter-presentation interval.

Actually it is not clear apriori what precise interval the animal's leave time measures since the animal could conceivably leave itself some margin for error in its own interval timer. Alternatively the animal could have a different model of the mechanism behind reward provision. However it is not unreasonable to believe that this margin should be the same from trial to trial with the same interval. This means even if the margin of error varies with the duration between food presentations (which if the animal knows about the increasing variability in its timing mechanism is sensible) we can still make useful comparisons between distributions of leave times corresponding to different inter-food times.

One might be tempted to argue that a patch which suddenly depletes is unlikely to be encountered in a natural environment. If resources within a patch are monotonically depleted during foraging the animal is forced to chose a time at which to leave the patch and travel to another which has a higher rate of reward if it is to sustain feeding at some overall average rate. The Marginal Value Theorem describes how an animal in such as situation can maximise its rate of reward. R, the rate of reward intake is the ratio of the cumulative resource acquired at a patch $F(t)$ and the time required to take the reward. This time is the sum of the time spent at the patch t and the time spent traveling to the patch from the previous feeding ground T.

$$R = \frac{F(t)}{T+t} \tag{1.7}$$

The time t^* at which the animal leaves the patch can be predicted if its aim is to maximise its rate of reward.

$$\left.\frac{dR}{dt}\right|_{t=t^*} = \frac{1}{T+t^*}\left.\frac{dF(t)}{dt}\right|_{t=t^*} - \frac{F(t^*)}{(T+t^*)^2} = 0$$

$$\left.\frac{dF(t)}{dt}\right|_{t=t^*} = \frac{F(t^*)}{T+t^*} \tag{1.8}$$

The optimal departure time occurs when the rate of return in any patch hits the global average rate of return across all patches. If animal is foraging optimally its decision to leave a patch should be made by comparing its estimate of the inter-reward period with its experience of the global average period across the patches it has previously visited.

1.4 Concluding timing phenomena

In this chapter we have briefly studied a bewildering array of phenomena which indirectly shed light on the means by which animals and humans perceive the passage of time over intervals of seconds or minutes. Of these, the scaling properties conferred by Weber's Law stands out. This law implies that the mechanism underlying time perception over many orders of magnitude is corrupted by multiplicative noise. This means that the noise in the timing circuits increases linearly with time.

We have also looked at defects in timing seen in Parkinson's patients which give more information about the perceptual mechanisms of time. In the next few chapters we will connect the mechanisms behind timing with which drive working memory and a see how the parkinsonian defects provide clues to the means by which learning, memory and temporal perception interact.

Chapter 2

Working memory timing in neural activity and models of neural data

Working memory is increasingly well understood as both a neural and cognitive phenomenon. In working memory information is stored, held, subsequently used to take an action and then discarded. (Most experimental paradigms ensure the information is of no use once a response has been made). Working memory has no useful purpose on a timescale beyond the end of a single experimental trial.

As the shortest term encoding process for memory, working memory is assumed to serve both longer term memory processes and decision making. It is critical to the study of timing because memory is invariably invoked in the psychological theories of temporal perception and because the processes of working memory occur on a very similar timescale to those of interval timing.

The generally agreed neural correlate of the cognitive function of working memory is sustained neural activity. Sustained firing of spikes is seen in many areas of cortex. Persistent neural activity observed in prefrontal cortex is least susceptible to perturbation by task irrelevant stimuli. For this reason prefrontal cortex is generally considered the locus of active working memory in the brain.

Working memory is important to the description of temporal perception because these two processes are both linked to the formation of optimal patterns of behaviour. Both are functionally important in describing a range of cognitive processes within a range between tens of milliseconds and tens

of seconds on the temporal spectrum.

Timing and working memory have been shown to share the same neural substrates. Lesion studies have shown that the prefrontal cortex is essential for accurate performance in timing tasks [26]. Recently it has been suggested that the dynamics of memory related activity in prefrontal cortex provide a representation of time[33].

This text will show that these two functions can be achieved simultaneously in prefrontal cortex without recourse to bistable neurons or explicit mechanisms with long, non-biologically plausible, time-constants.

It is therefore important to look at the phenomena of working memory in order to see what a joint theory of working memory and interval timing should be able to explain. Unlike many of the timing experiments described in the previous chapter the many working memory experiments test both an animal's behaviour and the observe specific electro-physiological responses. This has the advantage of opening up an insight into the underlying neurological basis of task related behaviour.

The results of an early example of such an experiment are shown in figure 2.1 and figure 2.2. In this experiment monkeys are storing a memory of the colour of a light they observed briefly at time zero. The graphs show the activity of prefrontal pyramidal cells over the course of many experimental trials.

At the start of an interval over which a memory must be held many cells are observed to increase their firing rate over that recorded in the inter-trial interval (the baseline firing rate). Over the course of the interval these cells reduce their rate of firing. Alternatively, some cells may increase their activity during the course of the same period. The peak activity for this second set of cells occurs at the point where the experimenter asks for the monkey to respond to the stimulus. These neural activations are seen repeatedly when the same or similar trials are repeated and are stereotypical to individual cells.

The firing patterns are termed persistent because they remain above baseline for much longer than the transient fluctuations typically seen in neural activity. Indeed in many cells the firing rate significantly exceeds the baseline level for the entirety of the memory interval.

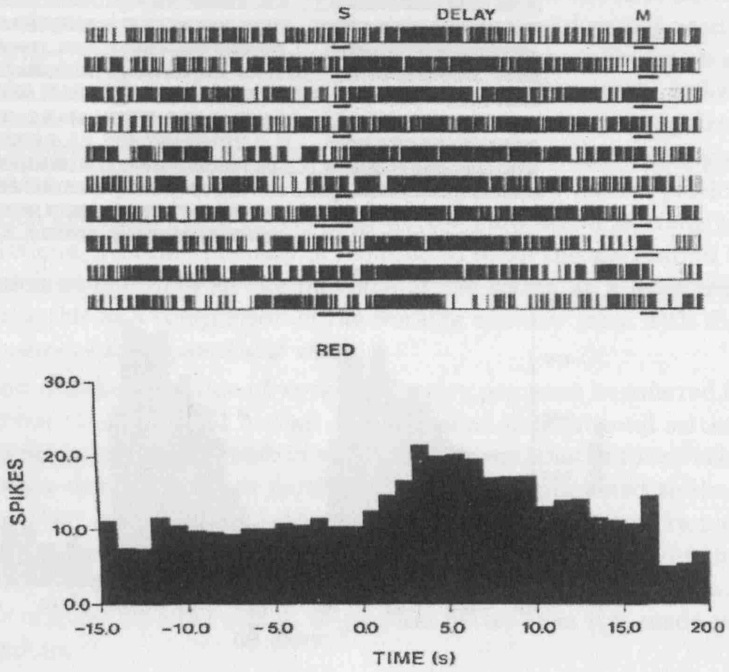

Figure 2.1: Early single cell recording in PFC during a DMS task showing a cell with a declining delay activity.

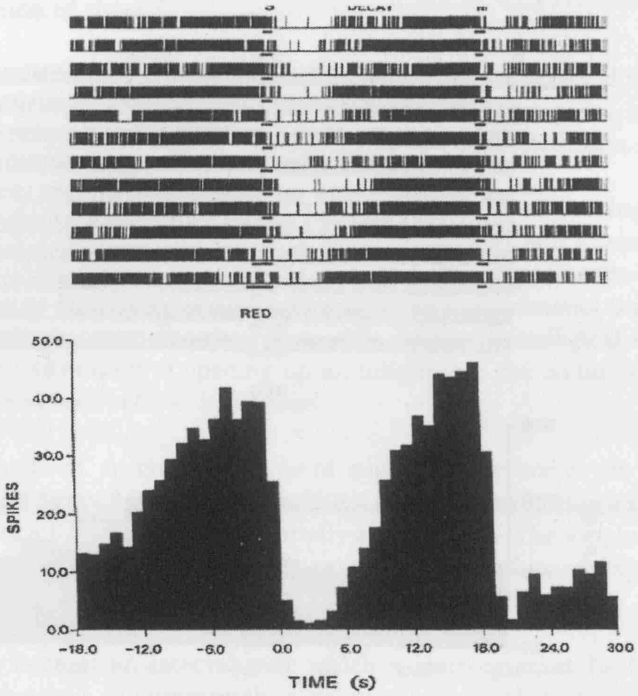

Figure 2.2: Early single cell recording in PFC during a DMS task showing a cell with a climbing delay activity.

2.1 Observing the behavioural correlates of working memory

The key to understanding the operation of working memory is its immediacy. The information stored in working memory has been recently obtained. This information is typically only useful to the animal for a short period after it is received and can be discarded at the end of the trial during which it was obtained. This does not mean that the animal does not need to learn from trial-to-trial. Longer term memories based on the information stored in working memory build up an animal's knowledge of the task. Indeed working memory could play a critical role in learning on a trial by trial basis. For instance one learning theory, reinforcement learning, strongly suggests that it is important for animals to keep a trace of the value a particular observation and subsequent observation for the purposes of learning temporal associations. Working memory is required to make the association between an action at one time an the outcome of the action at a later time. One can view this as a comparison of the working memory trace with the longer term memory for a particular value.

How can the operation of working memory processes be inferred from the behaviour of animal and human subjects in an experimental setting? One way is to give subjects a task in which the correct (that is to say reinforced) behaviour depends at least partly, on information presented to the subject at the start of each trial. At the time of the behavioural response this information is no longer available to the animal from its environment. In this way the animal requires some form of internal signal, in effect a memory of the original external signal, to perform better than if it made responses at random.

Working memory tasks differ primarily in form of the information which must be held and the observed behavioural response which signals correct memory retention. Either the subject is required to indicate what it experienced at the time of the initial stimulus at some later time or it is required to compare the initial stimulus to the response cue.

In all experiments undertaken with animals to date, a subject who has a full knowledge and experience of the task can be certain of the correct response as soon as the initial stimulus has occurred. However it is possible to imagine an experiment where the correct response is ambiguous during the memory delay. For instance an one might contrive an experiment with flashed light stimuli at the start and the end of each trial. The stimuli can either be a red or a green light. If both stimuli presented on a single trial

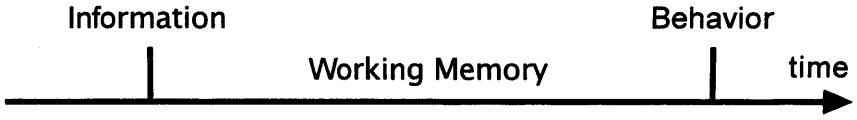

Figure 2.3: Time Line of Working Memory. Information is received via one or more sensory modalities. Behaviour critical content is stored until the a second stimuli is received which allows the correct behaviour to occur. Beyond this point there is no behavioural need for the subject to retain any of the information stored in working memory. This is not to say that retaining information about the temporal order of events in the task, the type of stimuli or the rewards gained on a trial does not occur or is not useful to the animal. Indeed this is subject with which reinforcement learning concerns itself. Note how this differs from data-acquisition trials in timing experiments where there is no second stimulus to prompt response.

are the same (both red or both green) the subject is trained to press the left hand lever. If the stimuli are different (one red and the other green) then the subject can not be certain of the correct response until the final stimulus has been shown.

2.1.1 Delayed match to sample tasks

Delayed match to sample (DMS) experiments require a non-continuous quantity or quality to be stored in memory [40, 22]. To successfully gain a reward the subject has to remember some feature of an initial stimulus which signals the start of a trial. This might, for instance, be the colour of a light or the shape of an object. There is then a delay of several seconds during which this information has to be retained to make the correct choice. At the end of this period a selection of stimuli, including that initially presented, is made available to the subject. The subject signals that the initial stimulus was correctly remembered by selecting it from the ensemble presented at the end of the delay. The trial then ends. Memorisation and recall may be made across sensory modalities. For instance the initial stimulus could be an object presented visually. The subject must remember its shape and make the match, at the end of the trial, via haptic clues [19].

Functional evidence of prefrontal involvement in working memory is provided by studies showing that cooling frontal cortex to 15 deg C leads to a reversible deficit in performance on DMS tasks [57]. The ability of a subject to complete the task correctly decreases in comparison to situations when the parietal cortex is cooled. Reaction times remain the same in all conditions.

2.1.2 Oculomotor delayed response tasks

A working memory experiment requiring the storage of a continuously valued parameter is the oculomotor delayed response task (ODR) [59].

In this task a monkey seated with its head fixed is presented with a fixation point. The animal must fixate on this point while a cue location is presented and subsequently removed as well as during a subsequent delay before the animal is permitted to respond. When the animal may respond the fixation point disappears and the monkey must make a saccade to the point at which the cue location was shown. (A saccade is an eye movement from one fixation point to another.) If the task is completed correctly the monkey is rewarded, see figure 2.4.

Should the monkey move his or her gaze to the correct point after maintaining fixation throughout the delay then the cue for the correct action must be internal. The correct saccade direction must be stored in working memory after the cue point vanishes.

Single cell recordings in the prefrontal cortex during ODR tasks show that populations of pyramidal cells encode the angle of the cue point from the fixation point. Individual cells are tuned for a narrow range of directions centred on the fixation point. For a given cell the magnitude of the sustained activity it displays during the memory delay peaks on trials in which the cue appears at the neuron's preferred angular direction from the fixation point. Should the cue appear at another angle, well away from this direction, then the change in the cell's firing rate during the delay will be negligible. Across the population of cells the full range of cue angles will be covered.

This spatial encoding is by no means the only method of encoding variables in sustained activity. Later parametric encoding of memory stimuli will be discussed in detail. This involves graded firing encoding salient aspects of continuously varying stimuli [7].

2.1.3 Comparison Tasks

A further development of the DMS task is the delayed comparison task. In this task the subject is presented with two similar stimuli. One occurs to signal the start of a memory delay; the other signals the end of the delay. The subject's task is to report which stimulus possessed more (or alternatively less) of the quality which differentiates the two stimuli. For instance, this quality could be the brightness of visual stimuli, the frequency of vibrotactile stimuli or the pitch of two auditory stimuli.

To date these experiments are carried out using fixed pairs of stimuli for the duration of training and testing. This renders the memory requirements no different to the DMS task since the appearance of the first stimuli fully determines the appearance of the second. Although it may make the task harder to learn. In an alternative experiment, yet to be performed with animals, the two stimuli could be chosen independently. This increases the working memory requirement since in this situation the subject cannot be sure of the required response until the appearance of the second stimuli.

2.2 The neural substrates of working memory

Sustained single cell activation is strongly correlated with the process of working memory [51, 50, 22, 20, 40]. From the onset of a salient stimulus

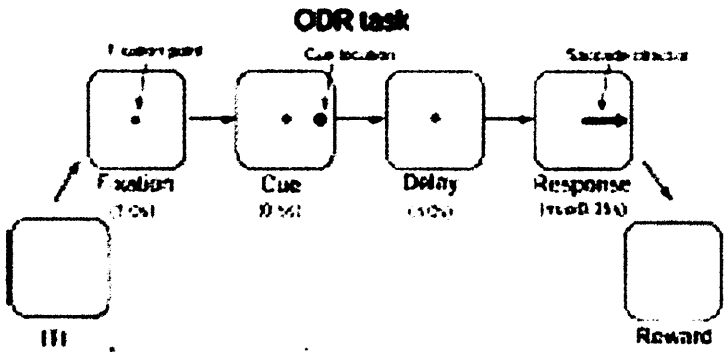

Figure 2.4: A schematic view of the oculomotor delayed response task. Trials proceed as follows. A fixation point appears alone on the screen in front of the monkey for one second. Then a cue point is displayed for half a second before disappearing to signal the start of a three second delay period. At the end of this period the fixation point, on which the monkey must remain focused until this moment, disappears and the monkey is required to saccade to the remembered location of the cue point. If the task is completed correctly the monkey gains a reward. [59]

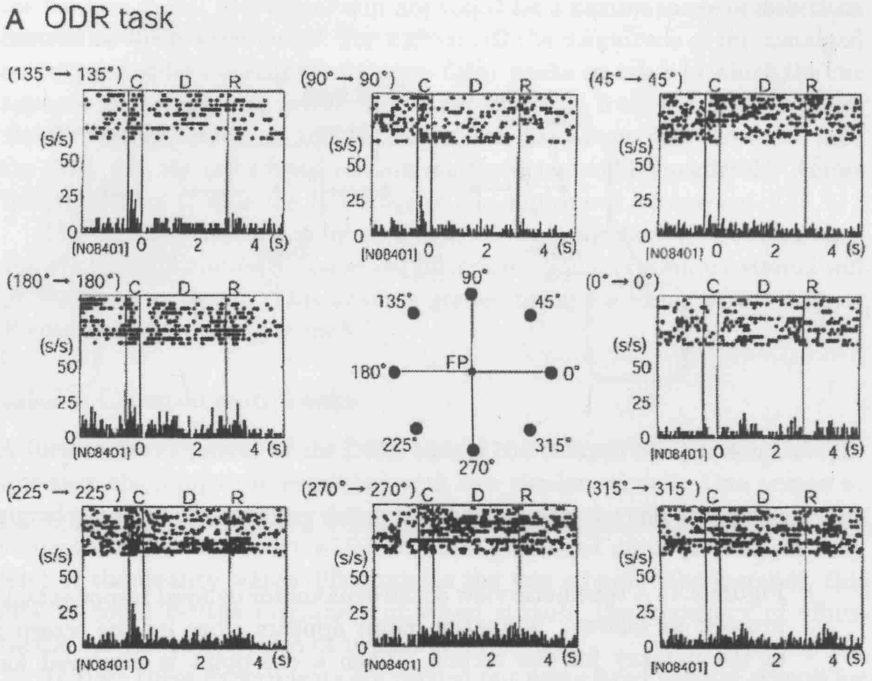

Figure 2.5: Cue dependent delay period activity in a prefrontal pyramidal cell during the ODR task. The neuron responded most vigorously when the cue was presented at 225 deg. Cues were presented randomly in the eight positions shown. [59]

pyramidal cells will show increased firing which persists until the animal acts on the information contained in the stimulus. In the case of the ODR task, described above, this information is the spatial angle for the correct saccade.

A cell will typically make a transient response to the initial task stimulus and then show a raised firing frequency of 5 to 8 Hz above its baseline firing rate seen in the inter-trial delay. In most cases this is not stable throughout the memory period. Sustained activity follows a cell and stimulus specific pattern of activity in which the firing frequency rises during the course of the delay, falls during the course of the delay or falls initially then rises at the expected termination of the delay.

2.2.1 Ramps and other features

The first clear evidence for dynamic working memory traces came from the work of Joaquin Fuster [22]. In his DMS experiment a monkey was presented with a coloured light, either red or green. After a delay of 16 seconds a red and a green light were presented as cue for the monkey to make a response. When the monkey chose the same colour as that shown to it at the start of the trial it received a juice reward.

The pyramidal cells which Fuster's team recorded reacted indifferently to whichever colour was presented. Other studies have shown persistent activity correlated with visual features in Inferotemporal Cortex [43]. The prefrontal neurons showed characteristic dynamics subsequent to the presentation of the memorised stimulus. On the basis of these temporal activity patterns cells could be divided into two classes. One class contained neurons which were excited at the time of the stimulus and subsequently decreased their firing rate as the delay period progressed. The other was formed from neurons which were inhibited when the stimulus was shown and then increased their firing until the time at which the choice was made.

The two classes could also be distinguished by their behaviour in the inter-trial period. This lasted 44 seconds, giving trials a back-to-back duration of one minute. Cells which ramped up in the memory delay also ramped up in the inter-trial period albeit at a slower rate. Conversely ramping down cells remained at base-line firing levels throughout the memory-free period.

Ramping activity clearly has the potential to act as a clock mechanism. If one or more cells ramp in a reasonably stereotypical, monotonic fashion between two events they can immediately be used to time the interval. Both cells which ramp up and cells which ramp downwards during the course of an interval can be used to estimate the time since the interval started.

2.2.2 Graded activity

In the work of Brody and colleagues [7] a monkey is presented with two vibrating stimuli separated by a memory delay. The monkey's task is to differentiate between the two frequencies pressing one of two levers if the second is a higher frequency that the first. Pressing the other lever signifies that the monkey perceives the first stimulus to have had a higher frequency.

Working memory is required in this task because the monkey must remember the frequency of the first stimulus over a delay before the second stimulus is presented for comparison. Neurons in prefrontal cortex recorded during this delay show sustained activity as expected. However the amplitude of the activity is conditional on the frequency of vibration of the first stimulus. This is important because it shows that prefrontal neurons are directly encoding task relevant parameters of stimuli in activity which is correlated with working memory.

Graded activity has been observed in two forms. One in which higher vibrational frequencies are represented by the upper end of the observed spectrum of sustained activity firing rates; the other where higher vibrational frequencies are represented at the lower end of the same spectrum. These are shown in detail in figure 2.6. The cell shown in this figure has a non-monotonic pattern of activity during the 3 second memory delay. Firing falls way after the transient associated with the initial stimulus before rising toward the time of the second stimuli. Graded persistent activity has also been seen in entorhinal cortex slice preparations [17].

Graded activity might appear to pose a problem for the association of working memory and interval timing process. If the magnitude of the persistent activity carries information about the some continuous quality of the presented stimulus how can it also reliably encode time? The observations of Brody's team show that there is redundancy in the coding of the working memory. It is coded with opposite polarity in different cells. This additional dimension means that a forward readout mechanism would be able to dissociate both the continuous timing signal and the stored working memory information.

2.2.3 Anatomy of prefrontal cortex

Prefrontal cortex comprises areas 8, 9, 10, 11, 12, 13, 44, 45, 46 and 47. These can be seen in Brodman's cytoarchitectonic map figure 2.7.

Direct projections to prefrontal cortex have been shown from the brainstem tegmentum, the pons, the hypothalamus and the amygdala. Projec-

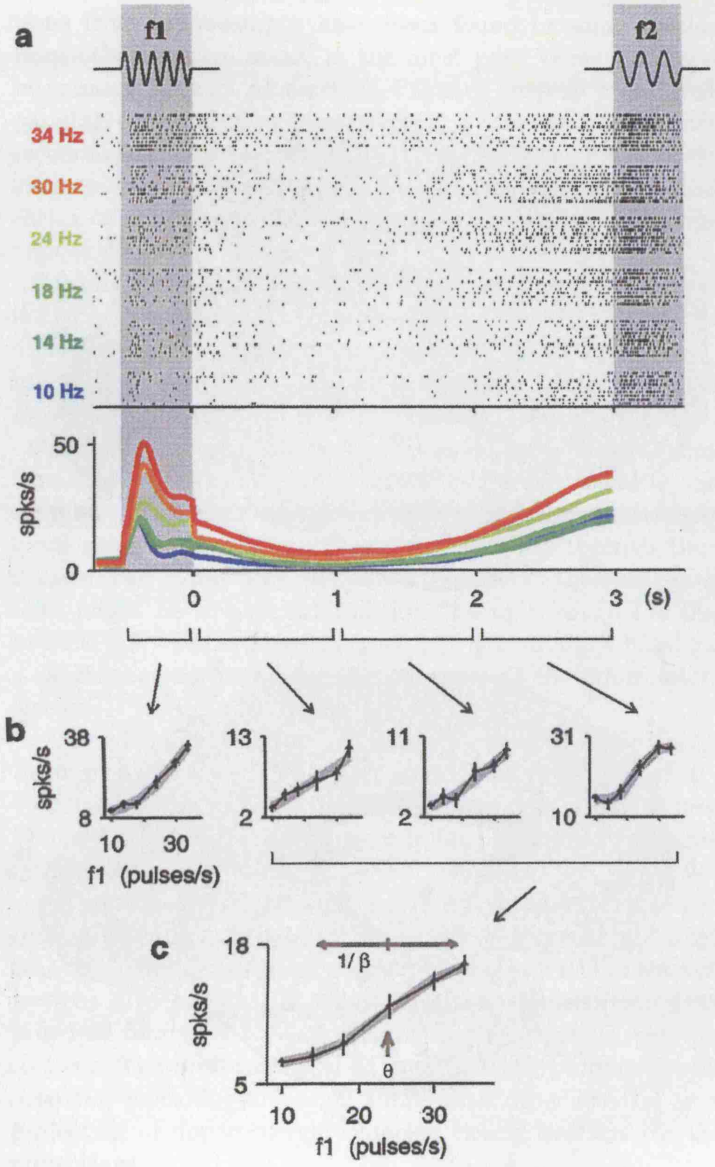

Figure 2.6: Persistent firing of a prefrontal pyramidal neuron. (a) Rasters: each row of ticks represents a trial and each tick an action potential. Trials were presented in random order but have been sorted here into blocks of equal f1 frequency, indicated at left. Colour code for f1 frequencies indicates corresponding smoothed peristimulus time histograms (PSTHs), shown below the rasters. (b) Firing rate, as a function of f1 frequency, averaged over different parts of the trial, indicated at the base of the arrows pointing to each panel. Notice the different y-axis scaling for each panel. Grey lines are sigmoid fits to data in each panel ($firingrate = a * \tanh[\beta(f1\theta)] + c$); error bars, in this and in subsequent figures, are standard errors. (c) Firing rate as a function of f1 averaged over the entire delay period. $\beta = 0.11$ s/pulse, $\theta = 24$ pulses/s.

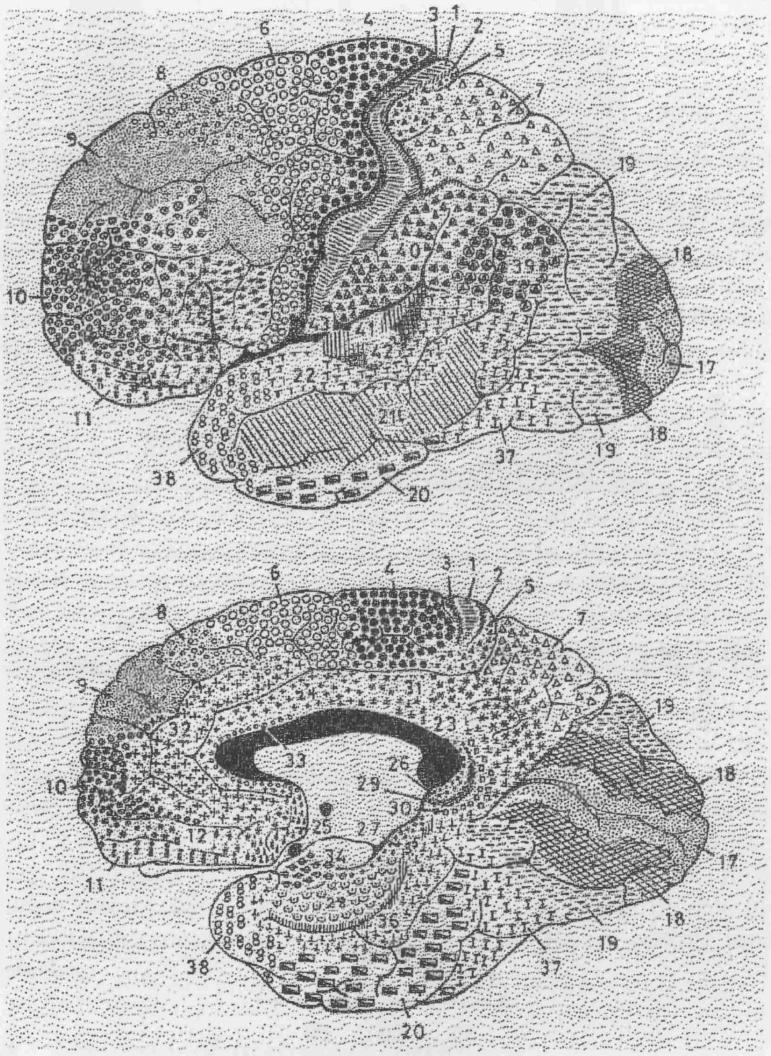

Figure 2.7: Brodman's map of cortex

tions from hippocampus have been found in some species. Connections from other cortical areas, in the most part, come from areas not involved in primary sensory processing. Primary sensory areas project to adjacent parietal, occipital or temporal cortex. These areas are connected to adjacent secondary regions but also project to discrete volumes of frontal cortex via long association fibres. These connections are reciprocated by the frontal cortex which sends afferents back to corresponding secondary processing regions [21].

It might be inferred from this that information reaching prefrontal cortex is highly generalised. It is therefore not unreasonable to model inputs from different sensory modalities with similar transient signals. The encoded information can be determined by various readout mechanisms of which more will be mentioned later in this text.

Indeed prefrontal cortex sends efferent projections to almost every structure from which it receives afferents. However there is one important exception. Basal ganglia receives unidirectional connections from PFC. The basal ganglia is connected indirectly to PFC through the thalamus. Because of this it has been suggested that one of the basal ganglia's functional roles might be to gate information flowing through the thalamus en-route to PFC [18]. Under this approach one can envisage basal ganglia providing a saliency signal regarding the relevance of the information in the sensory stream.

Acetylcholine, seretonin, norepinephrine and dopamine all have receptors in prefrontal cortex. The later stands out since prefrontal cortex appears to play a central role in the mesocortical dopaminergic system. More over Dopamine has a strong role in controlling how memory operates in prefrontal cortex [49].

Dopamine (DA) is a intermediate product in the synthesis of norepinephrine. It is formed in the cells of the substantia nigra and the ventral reticular tegementum of the mid-brain (VTA). These two regions' projections give rise to the mesostriatal and mesocortical DA systems. The principal targets of the later system are the piriform, entorhinal and frontal cortices. The prefrontal cortex is particularly prominent within these areas receiving more dopaminergic axons than other cortical areas. In fact the projection of dopaminergic synapses closely overlaps the thalamic afferent projections.

The dopamine receptor D1 has been shown to modulate working memory correlated activity in PFC [61]. Local release of D1 agonists, through iontophoresis potentiates sustained activity. Conversely D1 antagonists have the opposite effect.

Additional evidence for assigning the PFC a leading role in highest level brain functions comes from macroscopic anatomy. Simply enough, prefrontal regions account for increasing fractions of cortex with phylogenetic development figure 2.8. This is 29% in humans, 17% in the chimpanzee, 11.5% in the gibbon and macaque, 8.5% in the lemur, 7% in dogs and 3.5% in cats. If the volume of prefrontal cortex is plotted against total brain volume, a linear relationship is found. The significance of this that as phylogenetic development progresses less of the cortex is devoted to areas with specific sensory purpose.

The role of dopamine in prefrontal cortex has particular significance for the interplay of working memory, timing and long term memory.

2.2.4 Time and decision making

Consider an event which tends to occur at fixed time interval after an initial stimulus. An example would be the appearance of the yellow light an interval before the green light on a traffic signal. This event and the time at which it occurs is well predicted by the occurrence of the initial stimulus. Having received the first stimulus it should be possible to predict when the second will occur using memories laid down after previous observations of traffic lights.

Predictions such as theses allow animals to make decisions about the actions which they will take in their environment. Typically these decisions are motivated by the value of the eventual outcome to the animal. Naturally this is highly subjective. However is it assumed that food and drink are of value to all animals when they are not satiated. Such items presented to an animal are termed rewards. Under this assumption the goal of an animal is to maximise the rate at which it receives reward.

To do this animals need to be able to retain a memory of which actions lead to rewards with the highest probability in the shortest possible time. Algorithms designed to model this behaviour implicitly assume an accurate temporal kernel is available to correctly catalogue the time between salient events.

We know from the variability of interval timing experiments that no such system exists. Can these theories make use of variable temporal information or do they need to be superseded?

Theories which seek to explain how animals derive plans to maximise their rate of reward are collectively termed theories of reinforcement learning. The problem requires animals to integrate several sources of information to produce coherent signals upon which decisions can be based.

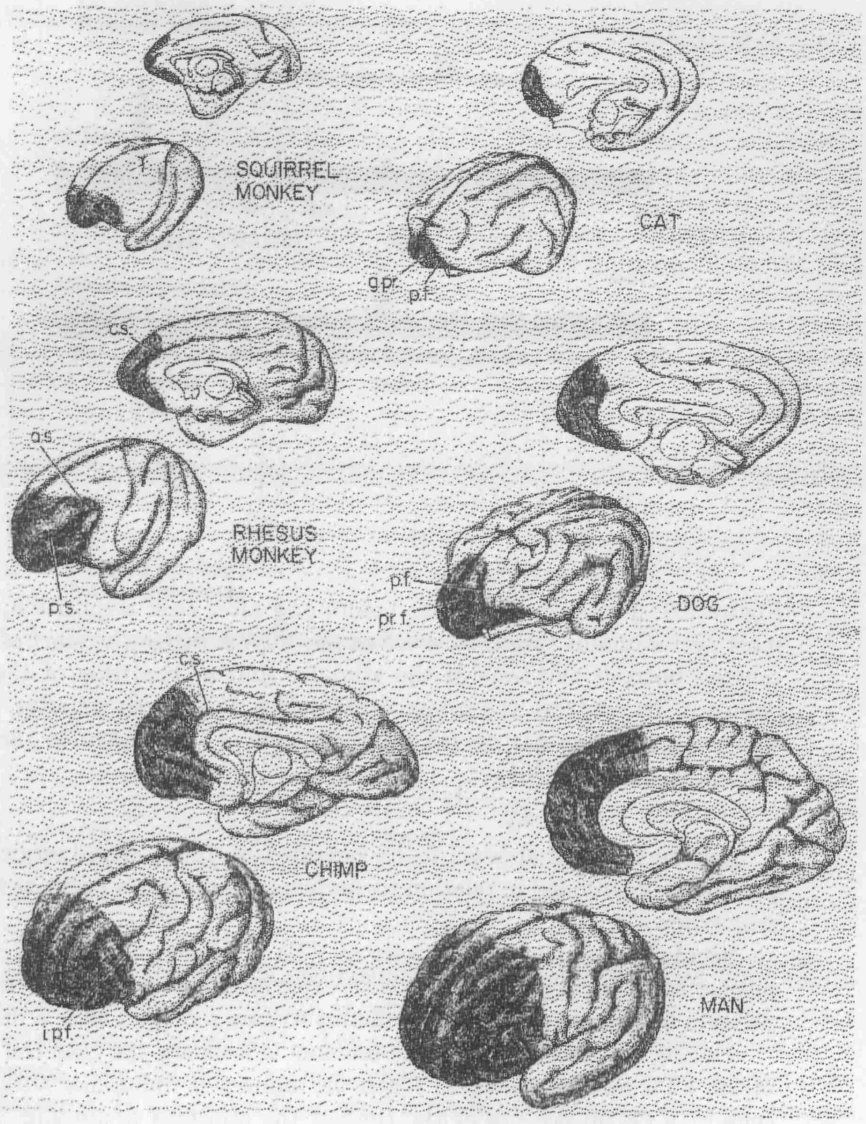

Figure 2.8: The development of prefrontal cortex Shaded regions denote prefrontal cortex in the brains of an number of mammalian species. The figure clearly shows the increasing importance of the region in higher primates.

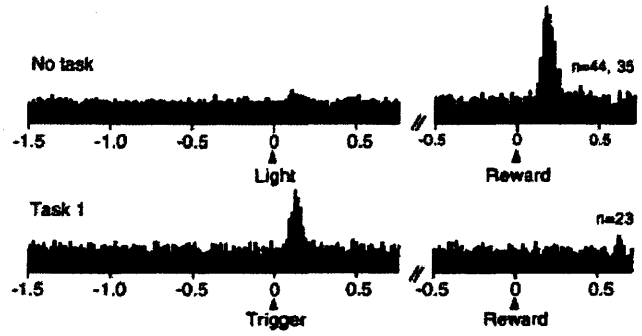

Figure 2.9: Firing in VTA cells before and after task acquisition. The up most peri-stimulus time histogram shows VTA firing at the start of training centred both at the time of the stimulus and at the time of the reward delivery. In contrast the lower figures show VTA activity after training. The peak response has moved from the time of the reward to the time of the initial stimulus. [54].

One such signal appears to be provided by the doperminergic system, previously mentioned in relation to studies of Parkinson's patients temporal perception.

Schultz [54] studied the activity in VTA of monkeys undertaking instrumental conditioning tasks. In these experiments animals were trained to respond to a visual or auditory stimulus to gain a reward after a fixed delay.

During the time in which the monkey is learning the task the response of the VTA neurons changes. When the monkey is unfamiliar with the task cells in VTA do not fire at the time of the stimulus figure 2.9. They fire strongly at the time at which an unexpected reward is delivered. Once the monkey is familiar with the task dopaminergic cells no longer respond to the arrival of a reward. Instead they fire above baseline at the time of the stimulus.

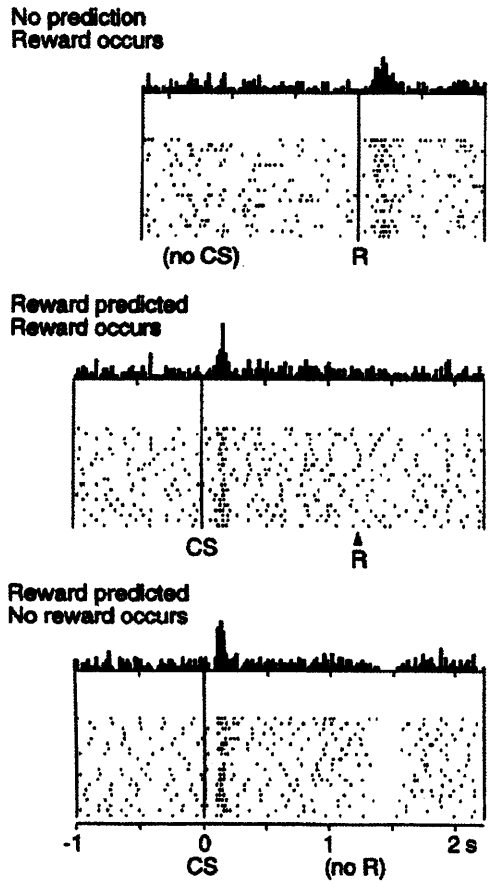

Figure 2.10: Single VTA cell responses to different prediction error contingencies The top most figure shows that a VTA cells burst when an unexpected reward is received. The prediction prior to this time would be no reward. The delivery of an unexpected reward gives rise to a positive prediction error. In the centre the reward is predicted by the conditioned stimulus. Thus there is no response at the time the reward is delivered because the prediction is correct. However the same response seen for the unpredicted reward is now seen at the time the conditioned stimulus is presented. This is because prior to the onset of the stimulus the animal had no information to predict a future reward and thus could reasonably expect no reward up to that point. Finally a predicted reward is with-held and at the time the animal predicted the reward the activity in VTA dips below baseline. In this case the prediction turned out to be optimistic and a there is a negative prediction error. [54]

The temporal difference (TD) theory of prediction learning shows how such a dopamine signal could be important for reinforcement learning. The aim of the theory is to explain how a prediction of future reward can be based on past experience. Three key quantities the stimulus $u(t)$, the reward $r(t)$ and the prediction $v(t)$ are expressed as functions of time within a single trial of the task.

It is proposed that the dopamine signal provides an on-going prediction error for reward. This means that above baseline firing in the VTA communicates a disparity between the reward an animal now expects and that which it had previously predicted. Firing drops below baseline in the event that a reward an animal was expecting is withheld, as shown in figure 2.10. This shows that in the absence of external signals the monkey is correctly timing the interval to the expected reward. If the duration of the trained interval was varied one would expect to see scalar noise in the dip below baseline.

The fact that each of these three quantities are functions of time is significant. It means that the theory assumes an accurate temporal kernel is available to cross reference each function. The description of TD will proceed with this assumption before we discus the problem of reinforcement learning with scalar timing.

Under TD the quantity the animal learns to predict is the total expected future reward for the trial 2.1.

$$\left\langle \sum_{\tau=0}^{T-t} r(t+\tau) \right\rangle \tag{2.1}$$

The average is taken over the trials of the experiment.

In classical conditioning which does not consider temporal displacements the Rescorla-Wagner rule is used to links individual stimuli with reward linearly via a single learnt weight.

$$\mathbf{v} = \mathbf{w} \cdot \mathbf{u}$$

If the appearance of stimulus u_i consistently predicts a reward simple learning rules can be used to drive the weight w_i toward one. On the other hand if u_i is paired with no reward w_i is reduced to zero. Despite its simplicity this rule can be used to explain associative learning in a wide range of conditioning experiments. Secondary conditioning is an exception because the rule prevents a second stimulus becoming conditioned with a reward when it is shown with a stimulus which already predicts the same reward.

If the two stimuli are temporally displaced this error is avoided with TD learning because it is able to take into account time dependent of stimuli and rewards.

Generalising to time dependent stimuli and rewards the discrete weights of the Rescorla Wagner rule become a kernel function. This allows 2.1 to be approximated using a discrete time linear filter.

$$v(t) = \sum_{\tau=0}^{t} w(\tau)u(t-\tau) \tag{2.2}$$

Minimising the prediction error 2.2 by stochastic gradient assent would update the kernel as follows.

$$w(t) \rightarrow w(t) + \eta\delta(t)u(t-\tau) \tag{2.3}$$
$$\delta(t) = \sum_{\tau} r(t+\tau) - v(t)$$

In order to use stochastic gradient ascent as outlined here knowledge of all future rewards available in the trial under consideration is required. This is clearly incompatible with the task. Instead we use an approximation which arises from the fact that $v(t+1)$ is an estimate of the average value of the total future reward expected based on previous trials.

$$\sum_{\tau=0}^{T-t} r(t+\tau) = r(t) + \sum_{\tau=0}^{T-t} r(t+\tau+1) \approx r(t) + v(t+1)$$

$\delta(t)$ provides the reward prediction error signal in the temporal difference algorithm. It is the sum of two components $r(t)$ the instantaneous reward received at the present time and the difference between the current predicted reward and that one step ahead $v(t+1) - v(t)$ 2.4 Using stochastic gradient ascent and the approximation to the reward one step ahead the temporal difference rule can be stated entirely using 2.3 and 2.4. It has been shown [44] that $\delta(t)$ under stochastic gradient decent behaves in exactly the same way as the dopamine signal over the course of a monkey learning the instrumental conditioning task figure 2.11 which also appears to signal prediction error.

$$\delta(t) = r(t) + v(t+1) - v(t) \tag{2.4}$$

This explanation for the role of dopamine requires an animal to be able to measure time within a trial in order to drive the prediction error signal.

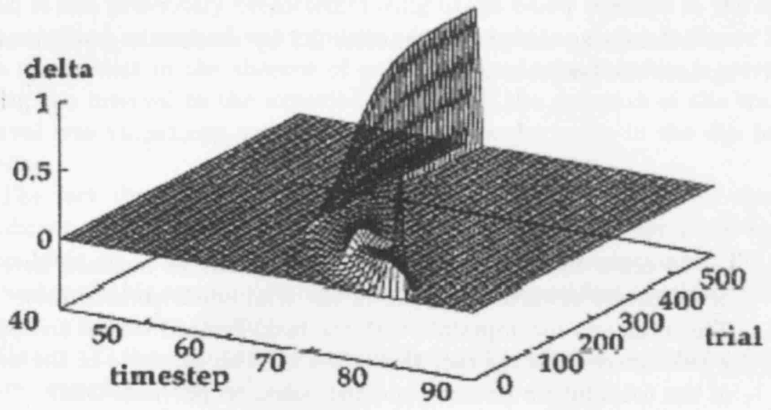

Figure 2.11: The results of simulated learning with the TD algorithm in the delayed response task. The δ peak moves back from the time of the reward to the time of the conditioned stimulus as the number of trials progresses. This is because the algorithm correctly learns the association between the conditioned stimulus as predictor of a delayed reward.

Animals do not time as accurately as the TD model supposes. What are the consequences of this for the model and for the reinforcement learning?

Recently, Daw [13] has proposed a partially observable Markov model of TD learning in trace conditioning. This model does not require an accurate timer to learn associations between conditioned stimuli and reward. Instead it holds that the animal perceives the world to be in one of two states. Correspondingly the animal has two internal states, which are labeled inter-stimulus interval (ISI) and inter-trial interval (ITI). Transitions between these states occur probabilistically. Conditioned stimuli strongly tend to transition the subject from ITI to ISI. Similarly the occurrence of a reward gives rise to a strong probability of transfer from ISI to ITI. In the absence of the occurrence of a reward the subject will make the same state transition probabilistically after some period of time.

With a timer subject to multiplicative noise this model successfully completes learning where the interval between the conditioned stimulus and the reward is short. However at longer time intervals where the variance of the clock is much larger the reward prediction error signal does not completely shift from the time of the reward to the time of the conditioned stimulus.

2.3 Models of persistent activity

Models of persistent activity frequently use the internal connection structure of prefrontal cortex to maintain activity induced by external connections from areas of sensory processing. While naturally failing to recover the detailed picture seen in anatomy, these models vary in the level of description they achieve. Generally the models discussed bellow only explain a subset of the phenomena associated with sustained activity and working memory.

Looking at the dynamics of sustained activity there is little evidence for a cellular state or set of states which encode a working memory. A line attractor model of cellular memory is more realistic. Working memory needs to be able to store both discrete and continuously valued information of a relatively abstract nature. It needs to be able to store and recall quickly and efficiently without long periods of training. This is extremely difficult to achieve in neurons which have discrete firing states.

In contrast Hippocampal short term memory has long been considered to be based on distributed patterns of firing across populations of neurons. These are described as the stable fixed points of a dynamic system. The position and composition of these fixed points is controlled by the synaptic strengths between recurrently connected CA3 pyramidal cells. This dynamic

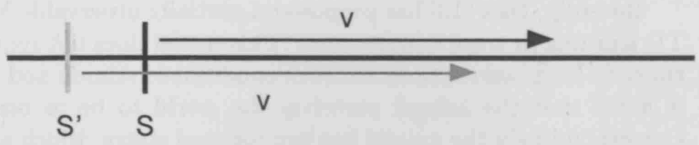

Figure 2.12: Motion along a line attractor allows additional situational information to be stored. For instance S and S' could be the starting locations coding frequencies f and f'. Activity moves along the line attractor with velocity v. Information about the elapsed time allows these two memories to be decoded accurately at any point. Alternatively the distance moved from the starting point could be a measure of elapsed time. Because these two advantages can not be found in the same system a distributed representation of line attractors are needed. This is seen in the delay activity of prefrontal cortex. Some cells re-scale the velocity with which they progress along the line attractor with the expected delay duration [7]. Others maintain a constant drift velocity.

system is highly suitable for information, which will be recalled many times. The spatial mappings of a foraging environment to specific groups of hippocampal cells is one oft cited example. In this case the memory of the spacial environment is encoded in the synaptic efficacies between cells.

In contrast information stored in working memory will only be recalled once. Typically the information will be used a short time after it has been received. A biological solution to this problem will be likely to place a premium on low energy costs, and the re-usability of the neural substrate. Maintaining high firing rates for long periods is metabolically expensive. Conversely a substrate which takes a long time to reset after storing an item is inefficient. Static attractors lose out on both these counts to line attractors [8].

Consider a memory encoded by a line attractor upon which drift occurs with a fixed velocity such as shown in figure 2.12. Without changing the dynamics of the attractor other items of information can be encoded separately

on the attractor by making use of the continuum of starting positions on the attractor. In both cases information about the time elapsed since stimulus onset can be measured from the distance along the attractor drifted by the memory state.

Later in this chapter we will see that a range of stimuli differing by a continuously valued parameter have been observed to be encoded in the sustained activity of a single cell. This is achieved by the cell scaling the frequency of its sustained activity with the continuous parameter.

Clearly a line attractor basis for memory is highly reusable. Many items can be encoded without changing the system dynamics which is costly in terms of both time and energy.

In contrast these are properties make line attractors distinctly unsuitable for long-term memory storage. Long term storage requires stability and low energy costs.

2.3.1 Memory as integration

It is instructive to consider the similarities between working memory, sustained activity and the process of input integration. A linear recurrent network can be created which integrates its inputs. The basic equation behind a linear recurrent network is given in equation 2.5. Here $\mathbf{v}$ is the activity vector of the network units, $\mathbf{M}$ is the symmetric recurrent weight matrix and $\mathbf{h}$ is the input vector.

$$\tau \frac{d\mathbf{v}}{dt} = -\mathbf{v} + \mathbf{h} + \mathbf{M} \cdot \mathbf{v} \tag{2.5}$$

The eigenvectors $\mathbf{e}_\mu$ of $\mathbf{M}$ define an orthogonal basis in which the network operates. They are defined in equation 2.6. The eigenvectors can be used to expand the activity vector $\mathbf{v}$ shown in equation 2.7.

$$\mathbf{M} \cdot \mathbf{e}_\mu = \lambda_\mu \mathbf{e}_\mu \tag{2.6}$$

$$\mathbf{v}(t) = \sum_{\mu=1}^{N_v} c_\mu(t) \mathbf{e}_\mu \tag{2.7}$$

Writing equation 2.5 in the light of equation 2.7 gives the following.

$$\tau \sum_{\mu=1}^{N_v} \frac{dc_\mu}{dt} \mathbf{e}_\mu = -\sum_{\mu=1}^{N_v} (1 - \lambda_\mu) c_\mu(t) \mathbf{e}_\mu + \mathbf{h} \tag{2.8}$$

This can be simplified by cross multiplying by a single eigenvector to take advantage of orthogonality.

$$\tau \frac{dc_\nu}{dt}\mathbf{e}_\nu = -(1-\lambda_\nu)c_\nu(t) + \mathbf{e}_\nu \cdot \mathbf{h} \tag{2.9}$$

Solving for the time dependent coefficients.

$$c_\nu(t) = \frac{\mathbf{e}_\nu \cdot \mathbf{h}}{1-\lambda_\nu}(1 - \exp(-\frac{t(1-\lambda_\nu)}{\tau})) + c_\nu(0)\exp(-\frac{t(1-\lambda_\nu)}{\tau}) \tag{2.10}$$

If one eigenvalue is 1 and all others are 0 then, the network will act as a perfect integrator of its inputs. This can be seen by considering equation 2.9 for the coefficient corresponding to the non-zero eigenvalue.

$$\tau \frac{dc_1}{dt} = \mathbf{e}_1 \cdot \mathbf{h}(t) \tag{2.11}$$

$$c_1(t) = c_1(0) + \frac{1}{\tau}\int_0^t dt' \mathbf{e}_1 \cdot \mathbf{h}(t') \tag{2.12}$$

If $c_1(0) = 0$ and $\mathbf{h}(T > t > 0) \neq 0, \mathbf{h}(t > T) = 0$, as might be the case for a transient sensory stimulus, then the activity of the network for $t > T$ is approximately as follows.

$$\mathbf{v}(t) \approx \frac{\mathbf{e}_1}{\tau}\int_0^t dt' \mathbf{e}_1 \cdot \mathbf{h}(t') \tag{2.13}$$

This is a time integral over the projection of the input onto the principal eigenvector. Activity in such a system persists well beyond the time of the input off-set.

Those looking for plausible biological integrators point out the difficulty of fine tuning the weights within a network to ensure that the principle eigenvalue of a recurrent weight matrix equals unity. Certainly there is no local synaptic rule which would lead to the required outcome because long-range interactions between connections are required. There is also no physiological evidence to suggest neurons have symmetric synaptic connections. Networks with principal eigenvalues which deviate from unity by a small degree show rapid decaying or accumulating behaviour. This occurs because the first term in equation 2.9 is non-zero giving rise to exponential increase or decrease in activity with time constant $(1 - \lambda_\mu)$.

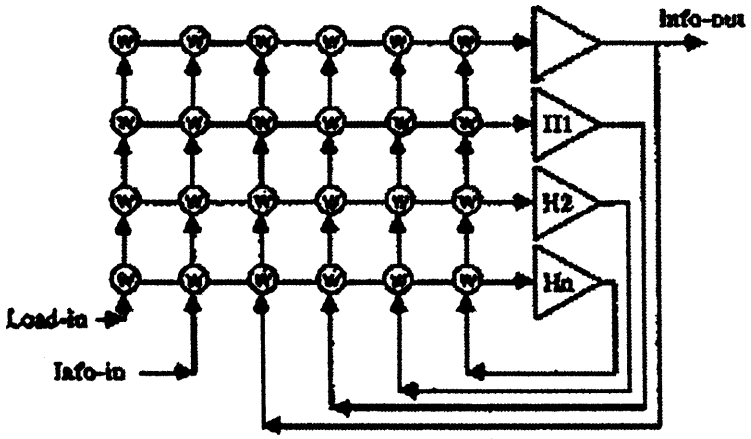

Figure 2.13: Schematic diagram of Zipser's network showing recurrent connections between four units one of which is an output. There are two external inputs marked Load-in and Info-in. These represent a binary gating variable and a random stream of continuous variables respectively. The network is trained so that The output unit holds the value of the sensory stream presented concurrently with a positive gate signal until the next gate signal is presented.

2.3.2 Basic network models and gating of information flow

One of the first models of Working Memory was that due to Zipser [64]. His simple recurrent model sought to resolve two problems. Firstly, how can a neural system retain a fixed memory after a the stimulus which formed the memory has gone or changed? Secondly how can the relevant sensory stimuli be selected from a stream of both relevant and irrelevant stimuli.

The model [64, 45] has a small population of recurrently connected sigmoid units. A single unit is designated the 'output' of the network. Two input streams carry sensory information and a gating signal. The sensory stream takes the form of a random number drawn, at each time step, from a uniform distribution on the interval (0,1). The gate signal is a binary variable taking the values zero or unity exclusively at each time step.

The connection weights in the network are learnt via back-propagation of errors [62]. Within this algorithm there is an error signal, the deviation of the output unit's value from the required value of the output. This is equal to the value of the sensory stream at the time step at which the gate signal was last unity. The aim is to get the output to hold the values of the sensory stream when the gate is unity and ignore the values presented when the gate signal is zero. In this way the system replicates the form of sustained activity during the time after a value is gated in while the gate is at zero.

Unfortunately the network requires many examples to be presented to it in training. It is incapable of retaining a stored value for many steps. The range over which it can hold graded inputs is limited. This reduces one of this model's major attractions - the ability to hold an item from a continuum in memory.

Perhaps the most important result of this model lies in showing how to extract salient information from a noisy input stream. It is by no means clear that this is something which occurs in prefrontal cortex. Several authors explicitly recognise the importance of the issue of gating, both in the context of modeling short term memory and in finding anatomical mechanisms by which selection may be achieved.

An alternative approach is to consider each unit of a feed forward network to be individually gated both at its input and at its output [29]. This implies some form of overwhelming top down control of information flow in the underlying network.

In contrast, proposed physiological mechanisms of gating have focused on the problem of controlling the information flowing to prefrontal cortex at an earlier stage so that irrelevant information never reaches the PFC. One

idea is that the basal ganglia, a mid brain region, which receives inputs from prefrontal cortex, controls information streaming toward the prefrontal cortex through the thalamus ensuring only salient items enter working memory [18]. Other authors implicate an mechanism modulated via neuronal synchronisation in sensory cortex [46].

Gating is not just an important issue for working memory. Timing mechanisms require start and stop signals to delineate salient stimuli between which intervals should be timed. This gate is explicitly referred to SET where it links the clock and accumulator units. In SET the gate controls what the amount of the timing signal stored in working memory.

2.3.3 Syn-fire chains and bistable units

Another mechanism for introducing stable patterns of activity in cortical networks which does not require the activity to be maintained by external inputs is the syn-fire chain. This is a feed-forward network in which groups of cells are connected in layers. Activity is passed down the layers synchronously. This means that spikes fired by neurons within an individual layer must cluster within a small temporal range to be passed to the next layer [15]. Sustained activity is maintained by closed loops in the chain. A stable attractor state is maintained as long as the total activity and dispersion of spike times from neural group to group remains within limits.

Syn-fire chains require more neurons than recurrent models of sustained activity and are vulnerable to noise because of the precise spike timing required to retain synchrony. Both Syn-fire chains and recurrent models of sustained activity require synaptic learning to deal with novel stimuli. This could be too slow to account for the ability to generalise learnt associations to novel stimuli rapidly.

Cellular bi-stability solves the problems syn-fire chains suffer when they encounter noisy inputs by allowing neurons to have two stable states. One in which the neuron is quiet, firing slowly. The other in which the neuron is firing rapidly. These are termed 'down' and 'up' states respectively. The up state might be sustained either in the presence of sufficient synaptic drive or in the presence of voltage or calcium gated membrane currents independent of synaptic input [53].

Bistablitity has not been observed in prefrontal neurons in awake animals although such effects have been observed in vivo in anaesthetised animals and in vitro in cortical slices [37]. Networks of bistable neurons require fine tuning to ensure, on the one hand, that not all the cells are recruited into the up state and that enough cells are in the up state to form a reliable

memory, on the other.

Another objection to bistable neurons is that they can not explain the graded persistent activity observed in prefrontal cortex and other parts of the brain [8]. Networks of bistable units with a graded component to their response require less fine tuning [35]. However they can experience discontinuous jumps in the firing rate for only small changes in their input.

Both syn-fire chains and networks of bistable neurons have been discussed as combined working memory and timing models by Fukai [33]. Unfortunately the syn-fire chain is unable to generate multiplicative noise and is thus out of step with psychological data on timing. Networks of bistable units are able to generate multiplicative noise [47]. However the neurons in the networks are unable to demonstrate the continuous range of firing between high and baseline activities seen in the previously presented electrophysiological data from working memory experiments.

One solution to this proposes bistable elements in the dendrites of neurons to increase the robustness of a neural integrator [27]. This model considers the firing rate r_i of neuron i to be a threshold linear sum of its tonic, dentritic and command (transient) inputs. The activity of individual neurons is now quasi-continuous.

$$r_i = \left[\sum_{j=1}^{N} W_{ij} D_j r_j + r_{ton,i} + r_{com,i} \right]_+ \tag{2.14}$$

$$\tau_{dend} \frac{D_j}{dt} = -D_j + f_j(r_j) \tag{2.15}$$

$f_{ij}(r_j)$ enforces bi-stability in the dendritic branches since it is equal to 0 until $r > r_{on,j}$ then rises to 1 before falling to zero again when $r < r_{off,j}$. The dendritic activation thresholds depend only on the presynaptic neuron. W_{ij} can be written in outer product form $W_{ij} = \zeta_i \eta_j$. In reality these assumptions can be relaxed somewhat. They are made for the purposes of analysis to render the network dynamics as a single equation 2.18. Under these assumptions 2.14 may be re-written as 2.16.

$$r_i = [\eta_i E + r_{ton,i} + r_{com,i}]_+ \tag{2.16}$$

$$E = \sum_{j=1}^{N} \zeta_j D_j(r_j) \tag{2.17}$$

E and r_i have a linear relationship because dendrites are successively recruited as the synaptic input, and hence the firing rate, increases. Combining 2.15, 2.16 and 2.17 gives 2.18.

$$\tau_{dend}\frac{dE}{dt} = -E + \sum_{i=1}^{N} \zeta_i f_i(\eta_i E + r_{ton,i} + r_{con,i}) \tag{2.18}$$

Stable points occur when E is equal to the final term. Hysteresis induced by the thresholding in the dendrites opens up a quasi-continuous band of stable points where the E nullcline crosses the flat nullclines associated with each successive dendritic branch recruited figure 2.14.

Other examples of a discrete approximation to a line attractor are given by Brody, Romo and Kepecs [8].

2.3.4 Bumps of activity

Another focus of efforts to explain sustained activity in the prefrontal cortex has been a set of stable states known as bump attractors. These are stable activity configurations between groups of excitatory and inhibitory neurons. Each population exists in a ring topography to enforce boundary conditions. A particular application of the bump attractor describes the storage of head direction variables in cells in the thalamus of freely moving rats [63]. Such models allow the integration of multiple information streams to build a continuously updated record of the animal's head direction in the horizontal plane regardless of its location.

The precise form of the bump of stable activity is determined by the distribution of excitatory and inhibitory synapses. One way to ensure a sustained localised bump of neural activity is to restrict the connections between excitatory neurons to a narrower range of neighbours than the inhibitory connections. It is argued that this is consistent with the anatomy of layers II and III of prefrontal cortex [28] where locally interconnected pyramidal cells are inhibited by wider arboured inhibitory basket cells.

An example of a bump attractor network used to explain the spatial coding of saccade location [59] is given by Compte et al [12]. Problems with bump attractors arise because of their inability to explain graded activity, and the fact that the bump becomes unstable in the face of spike frequency adaptation. The latter problem can be solved by introducing coloured noise into the network to prevent the position of the bump from moving too quickly [36].

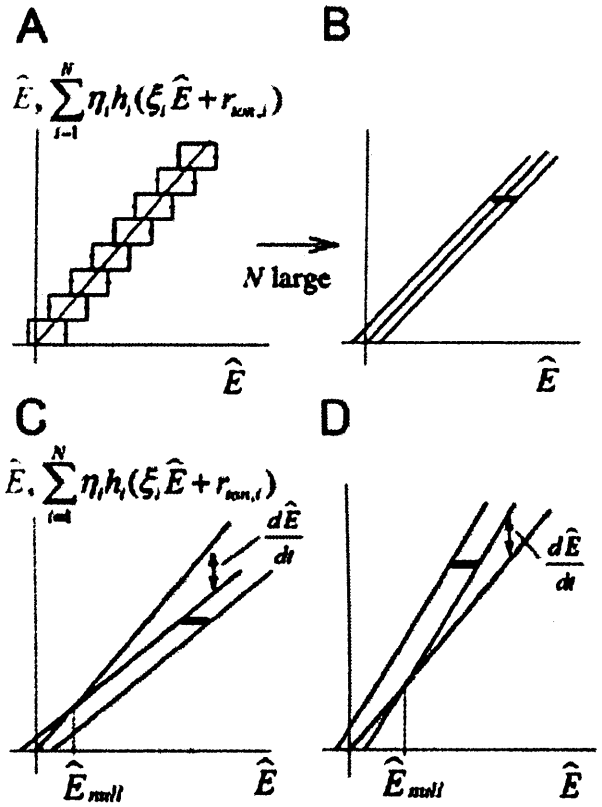

Figure 2.14: Nul-cline plots of quasi-continuous attractor. A) shows the hysteresis loops as successive dendrites are recruited to the system in while a stable balance is maintained. B) takes A) to the limit of large numbers of dendritic branches. C) and D) are examples of the drift that occurs at higher activations if the E nul-cline does not remain in the domain of the hysteresis loops. [27]

Moving bumps of activity can be used to explain the slow dynamics seen during working memory. On the level of a single cell one might expect to see a smooth gradation in activity over time as the activity peak moves through the population of which the cell is a member.

One advantage of the bump model is that it allows several bumps representing different memory items to coexist, spatially separated, in the same network. Another is that inhibitory signals are not needed to end sustained activity at the termination of a delay period. Instead transient synchronous inputs have been shown to halt sustained by rendering the excitatory neurons refractory simultaneously [28].

Recently models have begun to consider the dynamic aspects of sustained activity. Miller et al, [41], uses fixed sustained activity in a cell population to feed a population of integrators. These cells have firing rates which climb during the course of the fixed activity. In turn they inhibit the activity of a third population of cells which as a consequence have decaying activities over the same period. The authors use this model to explain the forms of graded persistent activity seen in Prefontal Cortex [7]. Stimulus encoding in the activity level of the constant sustained activity will be passed through to the dynamic populations.

2.4 Concluding working memory

The remarkable confluence of pathways onto prefrontal cortex a functionally non-specific region of the brain drives a key cognitive ability, the very short term retention of salient items of information. The quantity of information stored is comparatively small, scaling with the number of neurons. In longer term memory information storage increases with the number of synapses. Such as is the case in Hippocampal attractor based memory mechanisms. [50]. The power requirements per unit of information stored in sustained activity are considerable compared with pattern based memories since a population of cells is required to maintain firing above baseline for a period of many seconds. A pattern based memory requires no energy to be expended except at encoding and retrieval.

The role of Dopamine in controlling memory in PFC is particularly intriguing in the light of the theory, explained in the previous chapter, that dopamine signals a prediction error. One interpretation of the data from delay-match-to-sample experiments is that sustained activity represents a prediction of the correct response at the end of the delay [40]. This implies that activity in PFC increases as a task is learnt by an animal [2].

Activity based memory and the mechanisms behind it require a biologically and mathematically satisfactory account. As yet no agreement as to how information is encoded in sustained activity. Is the encoding spatial [51, 59], binary [5] or rate based [7]? Whichever encoding predominates, or if a mixture of all three types of encoding are used the neural mechanisms which support working memory storage can be used to perceive time.

Chapter 3

Sustained activity and time perception

In the previous chapter we have seen that following the presentation of the memory stimulus in a working memory task prefrontal neurons display an array of temporal activity patterns. These patterns repeat trial after trial and are collectively termed persistent activity. In this chapter it is proposed that these patterns form a temporal basis function representation of the time elapsed since the memory stimulus was shown.

An underlying line attractor mechanism for generating persistent neural activity, can be formed using a simple short timescale firing rule. This local rule ensures that the number of spikes within a recurrent network is tightly constrained.

Noise generated by probabilistic connections formed via unreliable synapses is multiplicative. Exactly the characteristic required for temporal traces which obey Webber's law. The network allows scalar time estimates to be made from dynamic working memory activity.

3.1 A model of timing from sustained activity

Sustained activity is modeled via a small recurrent network of binomial spiking units. The underlying ideas behind this network model are due to Shapiro and Wearden [56]. These cells are modeled at a coarse level of detail. No currents, thresholds, saturation points or refractory periods are modeled. Rather a simple overview of the dynamics of a recurrent network is used to demonstrate the fundamental dynamics of the network. This coarse scale view extends to the temporal scale. Time is discretised into relatively long

units each lasting 50 ms, approximately the length of the NMDA current time constant. Naturally each cell can fire several spikes in this period.

The most important feature of the network's dynamic behaviour is the unreliability of the recurrent connections between cells. This drives the variability in network activity. If neurons in their resting state lie close to their firing threshold then the arrival of individual spikes in the cells dendrites will cause the cell to fire. In this situation whether or not a cell fires given an incident spike is driven not but the cumulative inputs to the cell but the reliability of the connection transmitting the incident spike. These assumptions are critical in achieving output activity with the correct characteristics.

In the basic model [56] the number of spikes fired in the by a cell during each discrete time unit is equal to the number of successfully incident spikes. This implies that all the recurrent connections are excitatory. In the model presented here, Inhibitory external connections prevent some dendritic spikes from causing the cells to fire. Cells also have biases and which systematically render cells net spike sinks or net spike generators.

3.1.1 Network structure

The cells in the recurrent network are entirely excitatory and are connected sparsely (10 - 20% probability of connection between any two cells) via unreliable synapses. Unreliable synapses transmit an incident spike to the post-synaptic cell with a fixed probability γ. This probability is highly significant because of the assumption that the cells are close to their thresholds. Under this assumption a successfully transmitted incident signal will give rise to a spike at the post-synaptic cell.

In Shapiro and Wearden's model accumulator [56] the number of successfully received incident spikes in a discrete time period is equal to the number of spikes produced by the post-synaptic cell in the same interval. This allows a line attractor in the average firing rate over all the cells in the network to be constructed using a simple mechanism.

This is achieved by allowing γ for all the input synapses to each cell to vary as the inverse of the cell connectivity $C_i = \sum_i c_{ij}$ in equation 3.1. The cell connectivity is the proportion of the other cells to which a cell has a connection.

$$\gamma_i = \frac{1}{C_i} \tag{3.1}$$

Over a short period (typically on the order of tens of milliseconds) a

number of spikes $h(t)_i$ arrive at the synapses of a cell which is labeled i.

$$h(t)_i = \sum_{j \neq i} c_{ij} x(t)_i \tag{3.2}$$

The probability distribution over the number of spikes fired by the cell in the next period $P(x(t+\tau)_i)$ is given by a binomial distribution over the incident spikes parameterised by γ and $h(t)_i$ 3.3.

$$P(x(t+\tau)_i) = \gamma_i^{h(t)_i}(1-\gamma_i)^{x(t)_i - h(t)_i} \tag{3.3}$$

This mechanism ensures that a line attractor exists in the average firing rate of the recurrent network. More over the condition enforced by equation 3.1 ensures that noise within the network is multiplicative. The probability that a spike is transmitted from neuron j to neuron i is inversely proportional to the cell connectivity of the presynaptic cell. This means that the fewer connections to other cells a transmitting cell has the higher the probability that a spike transmitted by that cell has of being successfully received. The probability distribution of the network activity at time $t+\tau$ is rendered proportional to $< \gamma_i \gamma_j >_{ij}$.

3.1.2 Inputs to the network

Here the model deviates from that presented by Shapiro and Wearden [56]. The model has three external inputs. A temporal signal carrying stimulus information. An attentional signal which is constant and present only when memory is required. The final control is a tonic inhibitory signal which is constant for the duration of a single trial figure 3.1.

Each input consists of either excitatory or inhibitory spikes which are delivered randomly to cells in a recurrent network at a given average rate. The initial stimulus signal can be either excitatory or inhibitory depending on the network dynamics required.

The persistent inputs are not a form of sustained activity themselves. The spikes trains received by individual recurrent cells are independent and the spikes arrive randomly at a low fixed rate. For simplicity each input connection is reliable. This means that each excitatory input spike directly inputs a spike to the network. It does this by causing a cell to fire an extra spike. Similarly inhibitory spikes prevent a spike which would have been fired by a cell from being fired.

Networks giving rise to activity which is initially low but climbs, have to receive inhibitory signals to both set and reset their activity. On the other

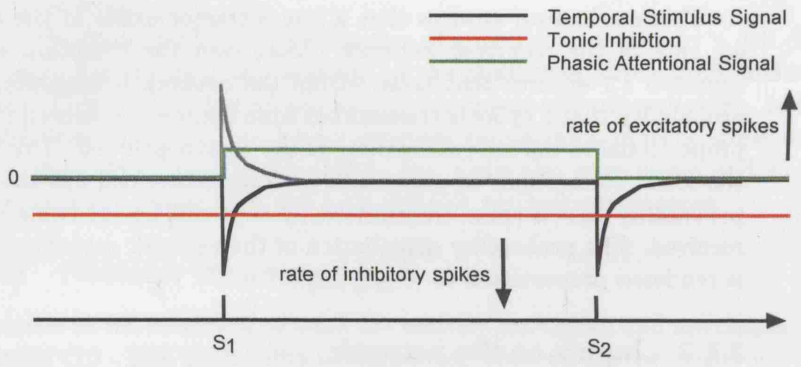

Figure 3.1: Stimuli are marked by transient signals, labeled in black. These serve to set or reset the network at the start and end of the memory delay respectively. Tonic inhibition, labeled red, reduces the overall firing rate. Release from inhibition is obtained during the memory delay via an excitatory attentional signal, labeled green.

hand, networks in which the cells show declining activity over time require an excitatory stimulus to start their activity pattern.

3.1.3 Dynamic activity - self accumulation and depreciation

A dynamic fixed point can be generated by allowing $h(t)_i$ to deviate from 3.2 for all or a number of cells.

$$h(t)_i = \sum_{j \neq i} c_{ij} x(t)_i + \alpha_i \tag{3.4}$$

$$\alpha_i = [-1, 0, +1]$$

If α_i is zero cell i obeys 3.2 and on average produces the same number of spikes as it receives. If a cell has $\alpha = 1$ it will, on average, produce more spikes than it receives from other cells. Such a cell is a net spike generator. Conversely if $\alpha_i = -1$ cell i will be a net spike sink. The sum of α_i across the network will determine whether the fixed point moves upward or downward with time. This is because positive $\sum_i \alpha_i$ leads to an excess of spikes being generated in the network which leads to self-accumulation; self-depreciation results if $\sum_i \alpha_i$ is negative.

The advantage of this approach is that it is robust. The downside is that the values of alpha must remain integers preventing fine tuning.

Alternatively if γ deviates slightly from equation 3.1 then the rate of progress along the line attractor can also be modulated, This is somewhat more delicate than using the binary α vector method to introduce self driven dynamics. This method of inducing self driven dynamics is less robust. It may be implemented through the following modification to equation 3.1.

$$\gamma_i = \frac{1 + \beta_i}{C_i} \tag{3.5}$$

β_i must be very close to zero if the system is to remain close to its line attractor.

3.2 Examples of working memory related sustained activity

The following examples seek to directly explain two different working memory experiments. The first is the Delayed Match to Sample task presented in the previous chapter. The second example models recent data taken from experiments which investigated the effect of varying memory delays. The

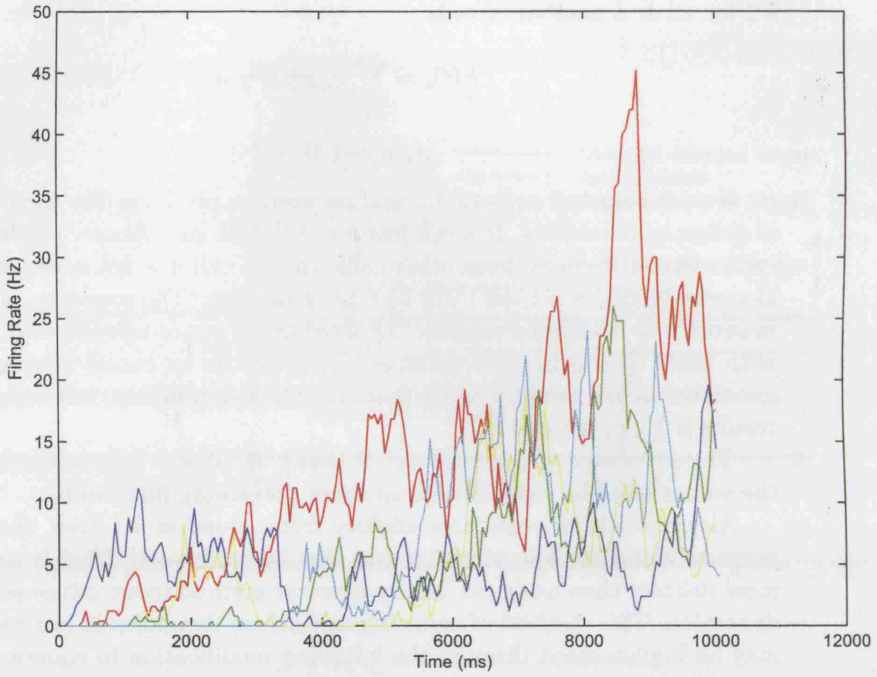

Figure 3.2: Average network activity in a system with $\sum \alpha_i = +2$ over 10 seconds. Trials begin with each cell silent. Firing is initiated by noise through the external inputs. Five trials are shown, each in a different colour. The network receives a tonic level of external input spikes. External inhibitory input is twice the external excitatory input. On average this amounts to 1 Hz and 0.5 Hz input to each cell respectively.

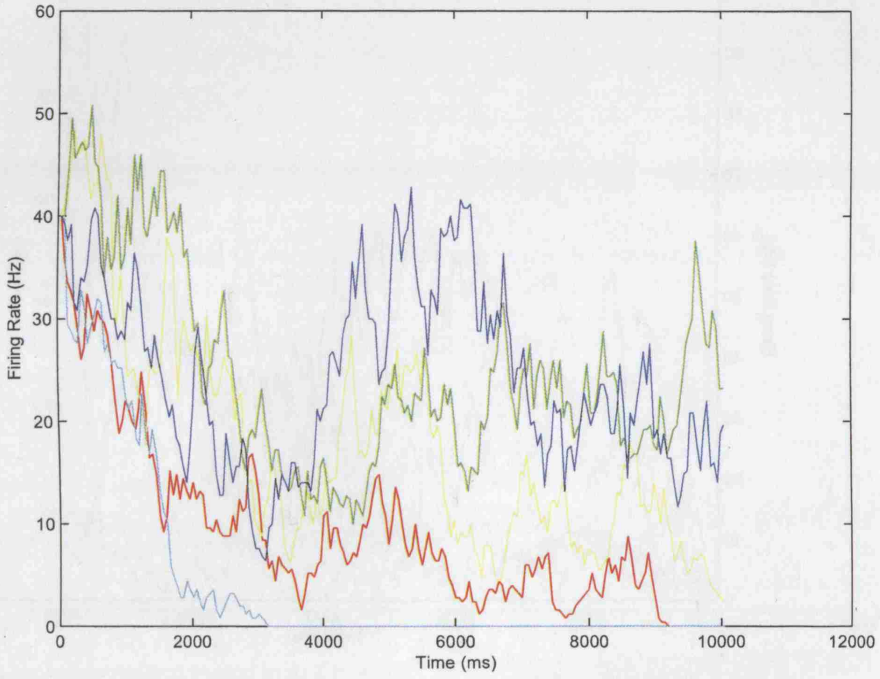

Figure 3.3: Average network activity in a system with $\sum \alpha_i = -2$ over 10 seconds. Each cell begins the each trial firing at 40 Hz. External inputs are at the same levels as figure 3.2.

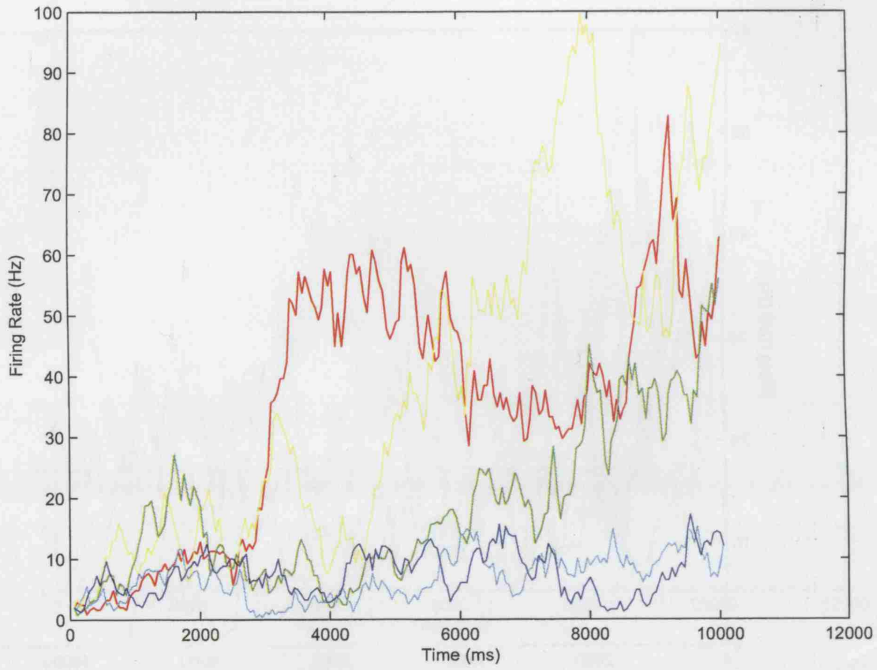

Figure 3.4: Average network activity in a system with $< \beta >= 0.001$, $\sigma_\beta = 0.002$ over 10 seconds. Note $\sum \alpha_i = 0$. Trials begin with five cells spiking. The level of the external inputs is the same as in figure 3.2 and figure 3.3.

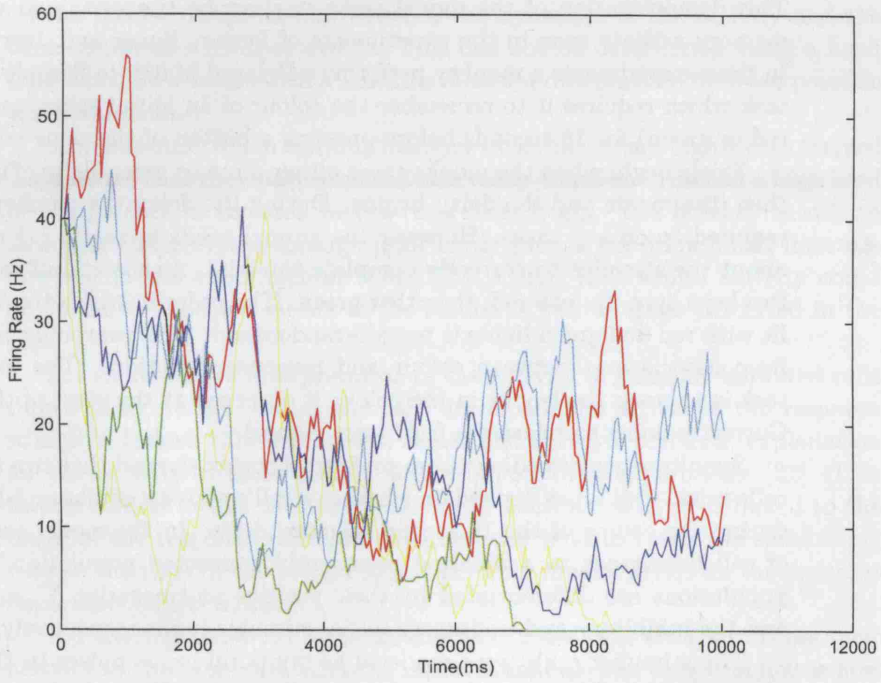

Figure 3.5: Average network activity in a system with $< \beta >= -0.001$, $\sigma_\beta = 0.002$ over 10 seconds. Note $\sum \alpha_i = 0$. Trials begin with each cell at 40 Hz. The level of the external inputs is the same as in figure 3.2, figure 3.3 and figure 3.4.

ubiquity of dynamic sustained activity across these and many other experiments varying task, sensory modality and time scales further demonstrates the potential utility of these traces for temporal perception.

3.2.1 Modeling a simple delayed match to sample experiment

This demonstration of the model seeks to describe the sustained working memory activity seen in the experiments of Fuster, Bauer and Jervey [22]. In these experiments a monkey performs a Delayed Match to Sample (DMS) task which requires it to remember the colour of an initial stimulus (either red or green) for 18 seconds before pressing a button of the same colour.

Trials begin when the monkey sees either a red or green light. This light then disappears and the delay begins. During the delay the monkey is not required to do any tasks. However the animal needs to retain information about the stimulus to correctly complete the trial. At the end of each trial two keys light up, one red; the other green. The order in which the keys are lit with red and green lights is pseudo-randomised. This prevents confounds from associations between colour and response direction. The monkey's task is to press the key lit in the colour it observed at the start of the trial. Correctly doing so releases a fruit juice reward.

Simultaneous recordings from prefrontal cortex showed that two types of cells exist. Cell types depend on whether a cell's activity climbs or falls away during the course of the 18 second memory delay. In the model each type of cell belongings to a different recurrently connected population. These populations are differentiated by their positive and negative $\sum_i \alpha_i$ values and the inhibitory and excitatory initial stimulus input respectively.

The stimuli signals were modeled as temporal input pulses to the populations which decay rapidly as shown in figure 3.1. The initial stimulus is excitatory for the $\sum \alpha_i < 0$ population and inhibitory for the $\sum \alpha_i > 0$ population. Both the level of tonic inhibition and the attentional signal remain constant.

Fuster observed no cells which coded for stimulus (or required response). Cells responded equally to both red and green stimuli. There is no explicit or implicit requirement for the animal to estimate time in this experiment since intervals are fixed across trials.

Figure 3.6 shows the results of the simulation compared with the experimental data. In this simulation time interval estimates are generated when the network activity crosses a fixed threshold. The distributions of time estimates produced by the model obey Weber's law. In order to correctly

model experimental situations the threshold for a particular fixed interval must be learnt by from the noisy working memory traces.

3.2.2 Modeling re-scaling in a comparison task

What happens when the time course of a working memory task changes? The interpretation of the sustained activity as a timing trace is dependant on the precise temporal link between the dynamics of the activity and the time course of stimuli or events. This can not be determined using a fixed trial schedule because such a schedule does not differentiate between possible temporal links.

Animals observed in working memory experiments are highly over trained. This means that they have seen the task many times and reached a high level of competence in the task before recordings begin. The monkey is able to anticipate later events through prior experience of the stimuli and intervals involved in the experimental task. This means that neural activity could be linked to expected events in the future as well as those perceived in the past.

For example one interpretation of the activity of stimulus inhibited cells shown in figure 3.6 is that the cells anticipate the arrival of the response stimulus. Indeed this was Fuster, Bauer and Jervey's preferred explanation for the activity of these cells in the results of their experiments [22]. This interpretation means that the peak in the neurons' activity is linked to the onset of the response stimulus. The neurons tend to reach the same firing rate at the time of the second stimulus. This time depends on the previous experience of the monkey.

An alternative would be to assume that these cells always increase their activity at the same rate after the initial stimulus. The temporal link is now to the first stimulus rather than the second. However, if this is the case and awkward question remains. If the response stimulus never appears after the initial stimulus will the activity of these cells climb for ever? Clearly there are refractory and metabolic constraints to prevent this from happening. In order to investigate this a working memory experiment with a variable delay is required.

Romo, Brody, Hernandez and Zainos trained monkey in a somatosensory frequency discrimination task. The task required information about perceived frequency to be held for a short interval [7].

The stimuli are chosen from a fixed set and presented to the monkey via a vibrating surface upon which one hand is fixed. The presentations last 500 ms.

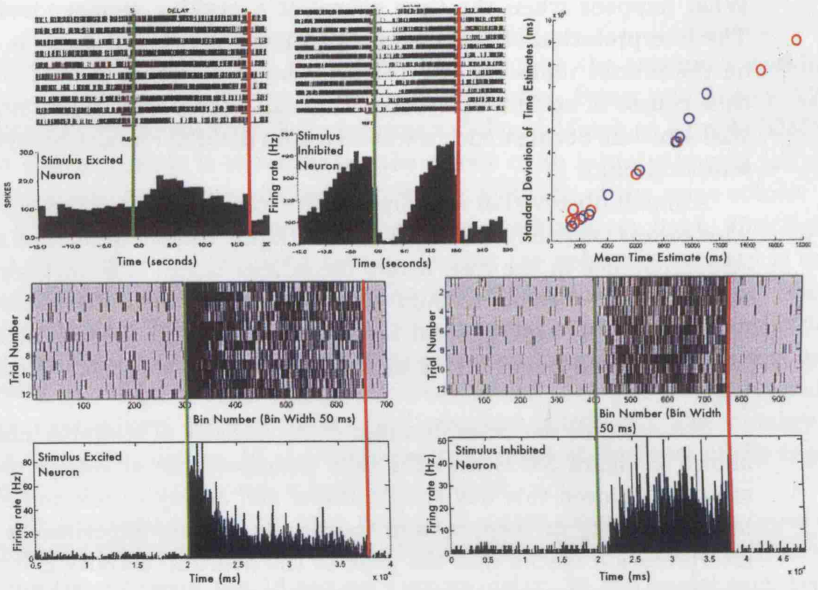

Figure 3.6: Experimental data and model comparison. Upper left plots show experimental peri-stimulus time histograms. Green and red markers show the start and end of the memory delay on each trial. The lower plots show the experimental simulation of the DMS data. Peri-stimulus time histograms are drawn up from the spike trains shown below each plot. Upper right plot shows the standard deviation of a several sets of time estimates plotted against the mean estimate. Each set of estimates was made by taking an arbitrary threshold through the network activity. Blue points denote estimates made from stimulus excited cells; red those from stimulus inhibited cells. Weber's law is clearly shown to hold among the estimates.

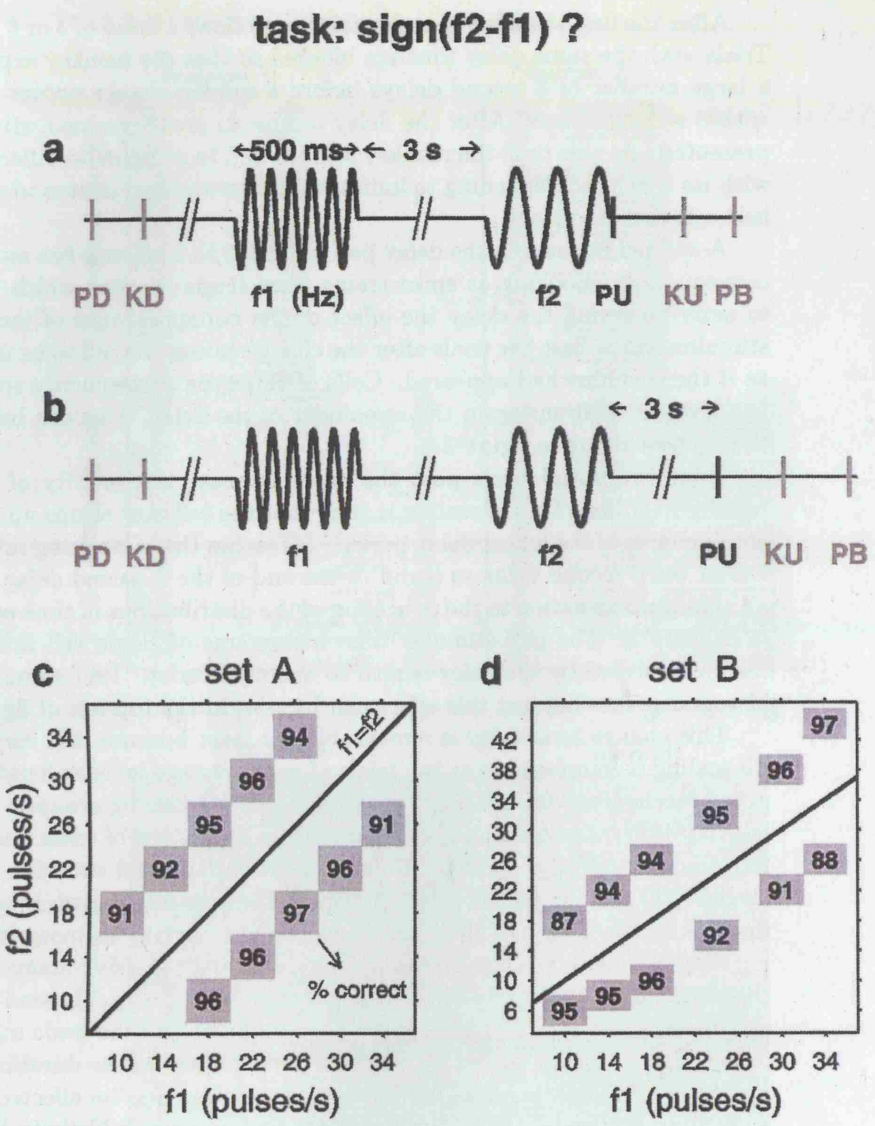

Figure 3.7: Behavioural task and stimulus sets used by Brody. (a, b) Sequence of events during the task. PD: mechanical probe moves down onto glabrous (hairless) skin of one finger of a restrained hand. KD: monkey's free hand presses key to indicate readiness for trial. f1: 500 ms long mechanical vibration, followed by a delay period, typically 3 s long. f2: 500 ms long mechanical vibration. PU: mechanical probe is raised, indicating that the monkey may now report its choice regarding the sign of f2-f1. KU: monkey's free hand leaves readiness key. PB: Monkey presses one of two pushbuttons to indicate its choice. (a) Standard task, used with four monkeys. (b) Task used with a fifth monkey. In this variant, there is a 3 s delay between the end of f2 and PU. (c, d) Stimulus sets used during recordings. Each grey box indicates an f1/f2 pair used; numbers inside grey box indicate overall percentage correct for that f1/f2 pair.

After the first stimulus of each trial there follows a delay of 3 or 6 seconds. Trials with the same delay time are blocked so that the monkey experiences a large number of 3 second delays before a sudden change occurs to trials with 6 second delays. After the delay a second, predetermined, stimulus is presented. At this time the monkey was trained to respond on different keys with its free hand depending to indicate whether the first or second stimulus had a higher frequency.

A sudden increase in the delay period from 3 to 6 seconds has interesting consequences. Looking at spike trains from single neurons which increase in activity during the delay the effect of the nonappearance of the second stimulus on the first few trials after the change causes the cell to be inhibited as if the stimulus had appeared. Cells of this type subsequently spike at a low level or ramp up again the remainder of the delay. This can be seen in the upmost figure in figure 3.8.

After the initial trials post the delay increase the activity of the cell rapidly re-scales. This re-scaling is such that the cell now ramps up over the entire course of the longer delay period. It reaches the same firing rate at the end of the 6 second delay as it did at the end of the 3 second delay. This is an analogous situation to the re-scaling of the distributions of time estimates in chapter 1. The peri-stimulus time histograms of single cell firing rates can be re-scaled by the delay length to exactly overlap. Peri-stimulus time histograms showing just this effect can be seen in the top left of figure 3.9.

This change in activity is remarkable not least because it is very rapid. Re-scaling is complete one or two trials after the change in delay length. Proposed mechanisms for effecting this change rely on altering synaptic weights [40, 52]. Such changes take time equivalent to many tens of trials and therefore seem an unlikely candidate mechanism for such a rapid and wide-ranging change [58]. In the model presented here, a simple mechanism is available for rapidly effecting re-scaling which relies upon working memory itself.

Working memory, encoded by sustained activity, can drive changes within the dynamics of timing traces through modulation the background level of excitation or inhibition. Specifically, if the amplitude of the tonic inhibitory noise input to the recurrent network is linearly related to the duration of the previously observed interval then re-scaling activity can be effected within a single trial of a change occurring. Since such a trace is likely to be noisy it may be desirable to average this duration over several trials (this is discussed further in chapter 4). The desired result is a progressive change over a very small number of trials after a change in interval length has occurred.

One method of achieving re-scaling is to link the degree of inhibition on a particular trial to the time measured on the previous few trials. In

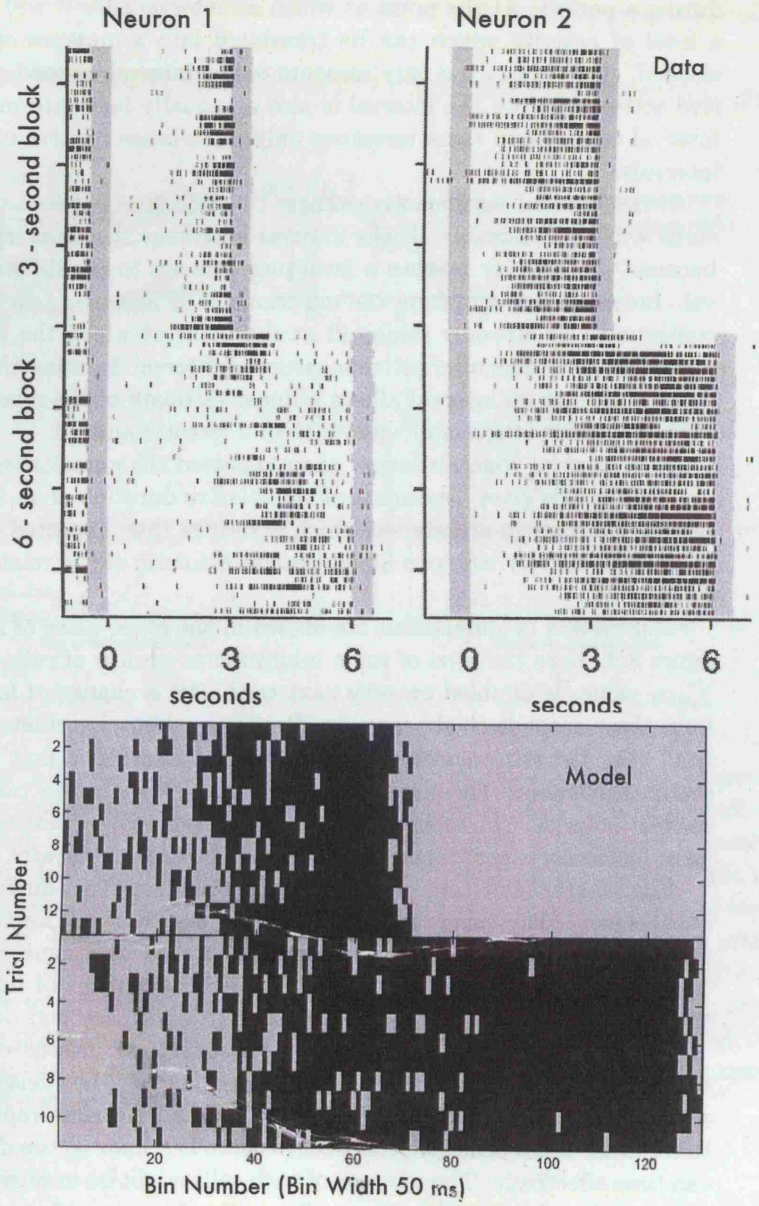

Figure 3.8: Experimental and model raster plots of showing activity re-scaling. Plots show spike trains on trials in time order, running from top to bottom, both prior to and following an abrupt change in interval duration.

the simplest case consider cell which times intervals by ramping its activity during a period. At the point at which an interval ends it will have reached a level of activity which can be translated into a measure of the interval elapsed. This is not the only measure of the interval elapsed. The cumulative activity during the interval is also an equally ligitmate measure of the interval time. Both these measures only make sense relative to other timed intervals.

If the interval significantly changes the difference between the time measures will be noticeable. If the interval lengthens the measure may not be because the activity reaches a level proportional to the difference in interval. Indeed it appears from the experiments of Romo and Brody that cells continue to be strongly inhibited at the point at which the interval is expected to end. The alternative measure of interval duration the cumulative activity during an interval allows a linear estimate of the relative length of both durations longer and shorter than a learnt standard.

In a interval which is longer than expected the cumulative activity of a multiple ramps gives a estimate of the relative duration of an the extension. On the contrary in an interval which is shorter than expected a single ramp to a lower activity will give an equivalent estimate of the relative brevity of the interval.

The results of simulations are shown in the lower plots of figure 3.8 and figure 3.9. Here the level of tonic inhibition to groups of cells with positive $\sum_i \alpha_i$ values is doubled on very next trial after a change of interval length from three seconds to six seconds. Rapid re-scaling is achieved within one trial. On the trial on which the six second interval is first seen activity climbs throughout the duration of the trial at the same rate as a three seconds interval. In reality this may be prevented by saturation or by a learnt inhibitory signal which shuts down the cells at a learnt duration.

Significantly only cells which increase their activity during the course of a memory delay seem to be affected by re-scaling. The time course of activation in cells which reduce their firing rate over time remains fixed. Two peri-stimulus time histograms on the upper right of figure 3.9 show this effect on a single cell over the course of 3 and 6 second delays.

It would seem that so far as time is concerned, these cells represent different aspects of time elapsed during the course of the delay period. Non re-scaling cells can be thought of a providing an invariant representation of time. Since these cells' activity decays there is a limit to the durations they can time effectively. The purpose of such cells might be to provide a frame of reference for the activities of re-scaling cells which are able to adapt rapidly to a wide variety of intervals.

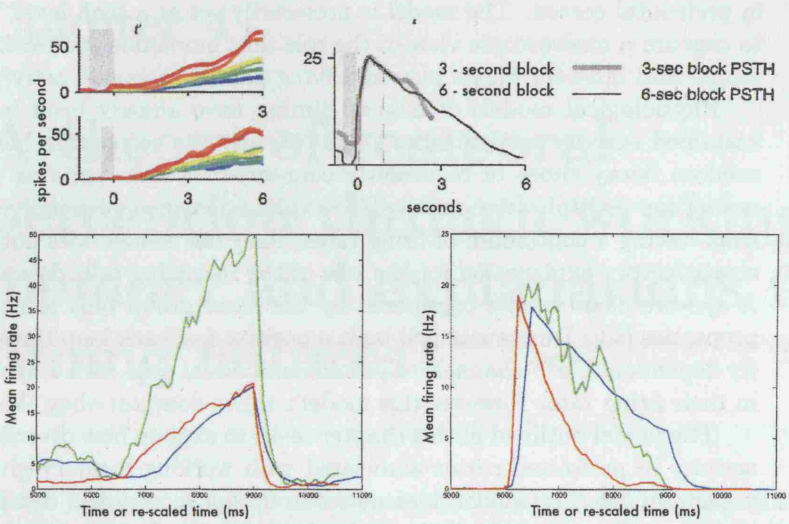

Figure 3.9: Re-scaling and non re-scaling sustained activity. Upper left shows complete re-scaling of graded sustained activity in a single cell with climbing activity. Upper right, a cell which does not re-scale its activity. Bottom left, average activity in a network receiving modulated tonic inhibition. Bottom right, simultaneous activity in a network of non re-scaling neurons. Blue activity - average over trials of three second delays prior to change. Green activity - mean firing rate during the first trial after the change to a 6 second delay. Red activity - average over trials of six second delays post change. Green and red activities over 6 seconds have been overlaid on the 3 second delay data for comparison. For this data each marked 1000 ms after 6000 ms is 2000 ms of real time.

3.3 Concluding sustained activity and time perception

In this chapter a case has been made for the inclusion of interval timing among the phenomena which arising from sustained memory related activity in prefrontal cortex. The model is necessarily set at a high level, but seeks to capture a macroscopic view of the role that unreliable connections, noisy inputs and inherent biases play in driving graded sustained activity.

Physiological models of interval timing have already been built using sustained activity mechanisms. Fukai [48] uses the correlation between the random decay times of recurrently connected bistable units as an explanation for multiplicative noise. This explanation precludes individual cells from having a continuum of firing rates. Also this model does not provided a satisfactory explanation for the role of the re-scaling cells detailed above. A syn-fire chain model considered by the same group fails to show scalar properties [33]. Durstewitz [16] built a positive feedback loop through activity dependent Ca^{2+} channels to provide individual cells with a line attractor in their firing rate. However this model's timer does not obey Weber's law.

The model outlined in this chapter seeks to explain how diverse dynamic activity in prefrontal cortex associated with working memory gives rise to scalar timing. The model does not contain any biophysical detail however it does make strong predictions about the state of pyramidal neurons in prefrontal cortex and the connections between them. The model predicts that cells are close to threshold. This means that a single spike successfully transmitted to a post-synaptic neuron has a high probability of causing the cell to fire. The other principle requirement is that the number of connections a cell receives is balanced by the reliability of the connections between cells.

In short cells with more connections from other cells have less reliable connections than those which receive fewer afferents. The means by which spikes percolate in a reproducible but noisy fashion throughout the models recurrent network is similar to the neural avalanches observed in cortical slices by Beggs and Plentz [3].

The percolation of spikes though a network via unreliable synapses is key to scalar variability in neural activity from trial to trial. Evidence for such variability in cortical spike trains has been observed by Shafi [55].

Chapter 4

A theory of temporal perception through working memory and explanations for timing failures

In the previous chapter arbitrary thresholds were used to show that sustained activity can provide time estimates which obey Weber's law. For the timing of specific task related intervals these thresholds must be learnt.

In experiments subjects signal that they are timing by changing their behaviour without cues as time passes during a trial, for example by uprating lever pressing in a Peak Interval task. Alternatively, in an Interval Timing task, estimation is demonstrated by taking a specific action to signal the end of a given interval. In order to learn the task both human and animal subjects need information to be feed back to them from the environment about the consequences of their actions. This might occur indirectly through the delivery or non-delivery of a reward. Human subjects can be given direct visual or auditory feedback.

4.1 Interval Timing in Humans

Interval timing is a standard test of cognitive faculties [10]. Typically subjects are asked to reproduce a fixed interval over many trials. During these trials they are occupied by a distractor task. Such a task may, for instance, involve reading out-loud numbers which appear at random intervals on a

screen. This task prevent the subjects from verbalising through counting. Verbalising allows estimates to become very much more accurate. This is because of the intrinsic rhythmicity of verbal phrases.

In figure 3.6 time estimates are made by the taking the point which the sustained activity passes a fixed threshold. In an interval timing task with human subjects the subject is asked to press a button when a fixed interval from the on-set of a stimulus has passed. On each trial after making their estimates feedback is given which informs the subject whether their measurement was above or below the target time. This information is binary. In a noise free situation it gives the direction in which the threshold should be moved to approach the optimal level but not how far it should be moved.

The simplest readout mechanism which uses binary feedback is a perceptron. A perceptron compares a weighted input to a threshold. If the threshold is passed then a response is made as described by equation 4.1.

$$\sum_i w_i * x(t)_i < \gamma \tag{4.1}$$

The time of the response t_{res} is the first time for which equation 4.1 holds. The weights and threshold are learnt by stochastic gradient ascent, updating on every trial.

Using this method with a network of non re-scaling cells, for simplicity, we are able to obtain time estimate distributions which closely correspond to those seen in the psychophysical experiments of figure 4.1.

$$w_i \rightarrow w_i + \frac{\eta}{2}(t^* - t_{res}) * x(t_{res})_i \tag{4.2}$$

$$\gamma \rightarrow \gamma + \frac{\eta}{2}(t^* - t_{res}) \tag{4.3}$$

t^* is the target time interval required in the experiment. This is the simplest of many learning rules which can be used to set the physiological threshold. Results for this rule used with modeled ramping down cells are seen in figure 4.1. Other equivalent mechanisms might be desirable depending on the type of information the subject receives from its environment.

4.1.1 Timing deficits in Parkinson's patients

Central to the descriptive power of the model is its ability to explain errors made by Parkinson's patients when they learn or reproduce intervals off medication. The most comprehensive psychophysical study of these deficits, involved separate groups of patients learning to reproduce time intervals

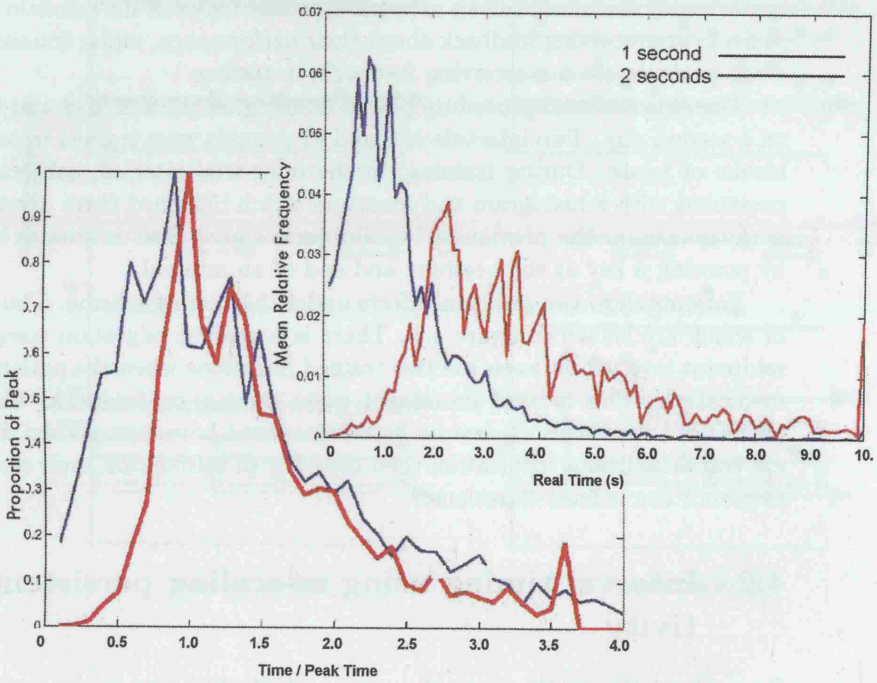

Figure 4.1: Data from fixed interval experiments shown normally (a) and re-scaled (b). Simulated data produced from learnt thresholds at 1 and 2 seconds, blue and red plots respectively, shown normally (c) and re-scaled (d).

while both on and off dopaminergic replacement drug L-Dopa [38]. The importance of these experiments is that they allow us to pull apart the role dopamine plays in learning time intervals and the effect it has on putative pacemaker mechanisms.

A two-by-two set of experiments and controls was used. Subjects were divided into four groups according to whether they were placed on medication during the time they were being trained to reproduce intervals and whether they were on medication during the testing phase of the experiment. Importantly this study allows us to differentiate between the condition when patients are receiving feedback about their performance, under training, and when patients are not receiving feedback, in testing.

The experimental procedure placed training on the first day and testing on a second day. Two intervals of 6 and 17 seconds were trained in separate blocks of trials. During training, in the inter-trial interval, subjects were presented with a histogram and messages which informed them about their performance on the previous trial. Subjects signal their estimates of time by pressing a key at the begining and end of an interval.

Patients show two principal effects under this testing scheme. The results of which are shown in figure 4.2. There is a general migration toward the midpoint interval between the two trained durations when the patient is off medication. This is most prominent when there is no feedback, when the patient is tested without first being administered Levadopa. When patients are trained without medication then tested with medication their estimates over-shot the trained durations.

4.2 Interval timing using re-scaling persistent activity

Re-scaling cells rapidly adjust the rate at which their activity increases with the delay interval in a working memory task. Because of this they are ideally suited to providing a functional representation of a time interval. Averaging over multiple trials, the activation of these cells reaches the same level at the end of the trial independent of the interval.

In order to use a group of such cells to time a fixed interval a threshold readout mechanism must be learnt. The great advantage of this threshold coupled with the re-scaling mechanism is that the threshold does not need to change between to intervals if activity is re-scaled between them. This means that subjects should be able to flip rapidly between accurate reproduction of two or more learnt intervals to which the required response is similar.

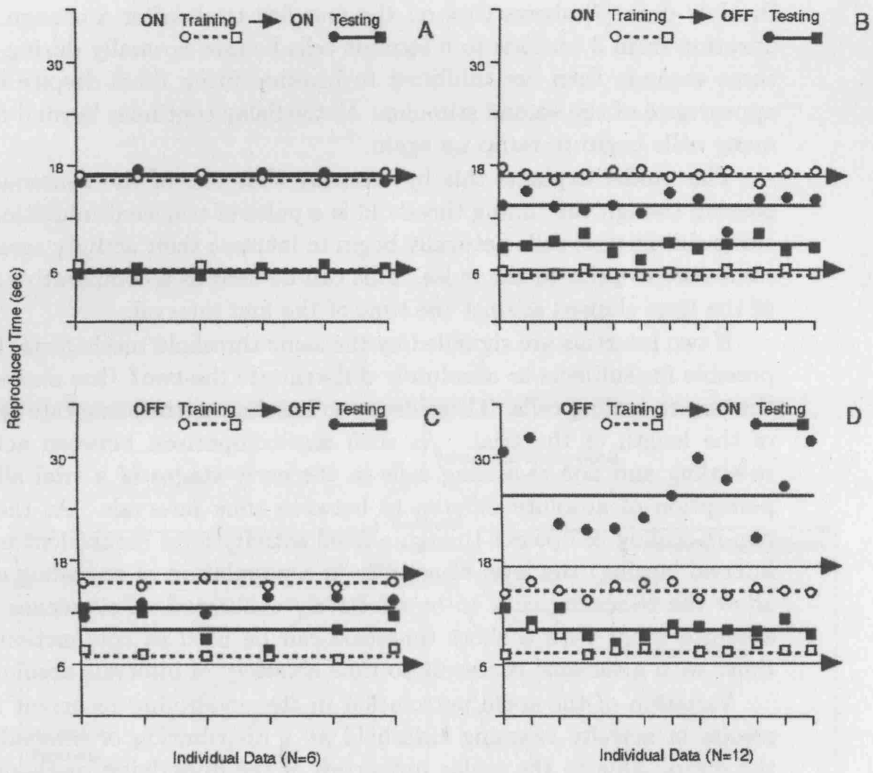

Figure 4.2: Plotted are the median estimates for all individuals in the each of the four groups of patients. Open points are time estimates produced in training; filled points are estimates produced in testing. Two general effects can be observed. Estimates migrate toward a time between the two standards when off medication. This effect is greatly enlarged when no feedback is given. Secondly when trained off medication but tested on medication patients over estimate intervals. This effect is largest with the longest of the two intervals. Data from [39].

Re-scaling activity requires animal to be able to time the difference between two intervals. This could occur via any of a number of mechanisms. One of the simplest is to use the integrated activity of the re-scaling cells. Brody's data [7] shows that on the first few trials after a change of delay duration from 3 seconds to 6 seconds cells behave normally during the first three seconds then are inhibited to baseline firing rates despite the non-appearance of the second stimulus. As the delay continues beyond this time many cells begin to ramp up again.

The model explains this by ensuring that one of the consequences of passing though the timing threshold is a pulse of transient inhibition. After this point in time cells naturally begin to increase their activity again at the same rate as prior to the pulse. This can be used as a comparative measure of the time elapsed against the time of the first interval.

If two intervals are signalled by the same threshold mechanism, how is it possible for subjects to absolutely differentiate the two? One answer lies in the non-re-scaling cells. These decay to baseline at the same rate regardless of the length of the trial. As such any comparison between activity in re-scaling and non-re-scaling cells in the early stages of a trial allows the perception of absolute differences between time intervals. At the time a non-re-scaling cell passes though a fixed activity level (equivalent to a fixed interval lapsing) the level of activity in a population of re-scaling cells will allow the re-scaling cells to be effectively calibrated. This means that an absolute timer with a short timescale can be used in conjunction with a timer with a variable timescale to time a variety of intervals absolutely.

Variation of the spike percolation in the underlying recurrent network results in activity reaching threshold at a distribution of intervals about the mean. Due to the scalar properties of the underlying mechanism this distribution has a standard deviation which is proportional to its mean.

The assumption is made that while learning a single interval the threshold is adjusted via the feedback on individual trials to capture the most accurate estimate its timing cells can make. The learnt threshold will correspond to that which on an average trial corresponds to the learnt interval.

It is relatively easy to learn a threshold by adjusting connections between the pyramidal cells and the readout according to feedback about the difference between the time estimate T_{est} and the presented interval T. A simple trial-by-trial update rule is presented below.

$$w_{i+1} = w_i + \eta * (T_{est} - T) \tag{4.4}$$

The distribution of threshold crossings should correspond directly to

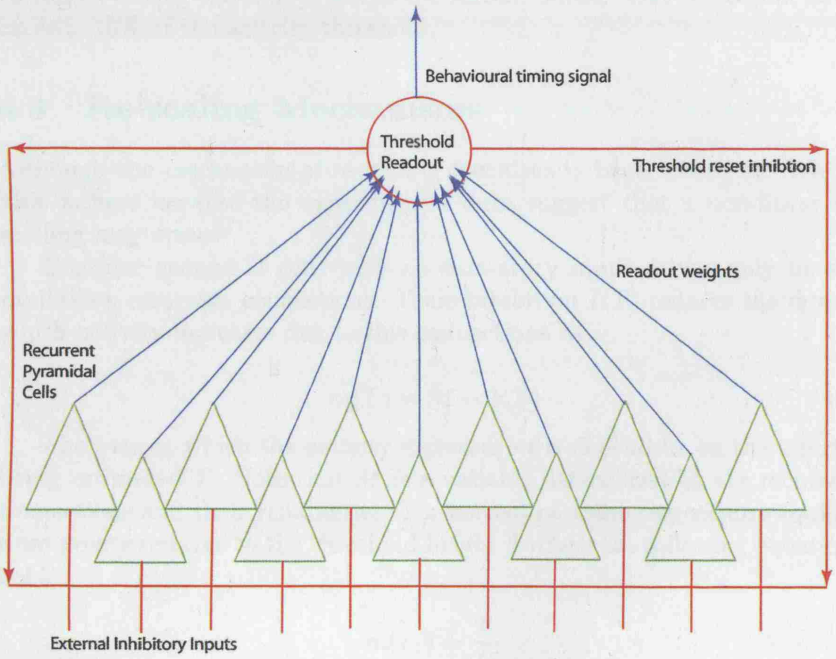

Figure 4.3: Network architecture showing recurrently connected pyramidal cells controlled by input inhibition and resetting inhibition from the readout mechanism. The effective level of the threshold can be adjusted by modification of the weight between the recurrent cells and the readout. An estimate is made and resetting inhibition initiated when combined activity from the set of recurrently connected cells exceeds the threshold. Re-scaling is supported via external inhibitory connections.

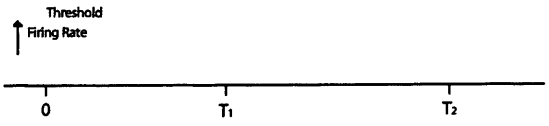

Figure 4.4: Re-scaling activity allows a single threshold to be used to make temporal discriminations. It also allows a far greater range of intervals to be timed than activity which has a unique time-course or which decays away during the to-be-measured interval.

distributions of time estimates taken from Peak Interval or Interval Timing experiments. This is because the Threshold read-out provides the subject with a direct timing cue which can be used to form the behavioural timing response.

Figure 4.5 shows a frequency distribution of time estimates at the time resolution of the underlying sustained activity mechanism, 50 ms. Intervals of 3 and 6 seconds have been learnt using a single threshold and a re-scaling mechanism described in the next section. A small, randomly chosen, selection of the activity traces used to build up this distribution is shown in figure 4.7. Although the traces giving rise to the two distributions are shown on parallel figures the thresholds are almost identical. This is because in this simple simulation we have not attempted to learn the re-scaling parameters. Instead the parameters controlling the magnitude of the re-scaling inhibition have been chosen roughly and the model has made small corrections to the threshold during the time it learnt the second phase. This correction never exceeds 10% of the activity threshold.

4.3 Re-scaling Mechanisms

Although the mechanism of re-scaling has already been looked at. We re-visit it here because the experimental data suggest that a non-linear re-scalling may occur.

Consider groups of cells with no excitatory input driven only be self excitatory recurrent connections. Tonic inhibition $I(T)$ reduces the rate at which activity increases due to this connections M.

$$m(T) = M - I(T) \tag{4.5}$$

The rate at which the activity increases m is dependent on the interval being estimated T. Note that M is a variable determined by the recurrent connections and their reliabilities. For correct re-scaling we require equilibrium points relative to the threshold height θ where the following equations hold.

$$m(T_1) = \frac{\theta}{T_1}$$

$$m(T_2) = \frac{\theta}{T_2}$$

$$T_1 M - T_1 I(T_1) = T_2 M - T_2 I(T_2) \tag{4.6}$$

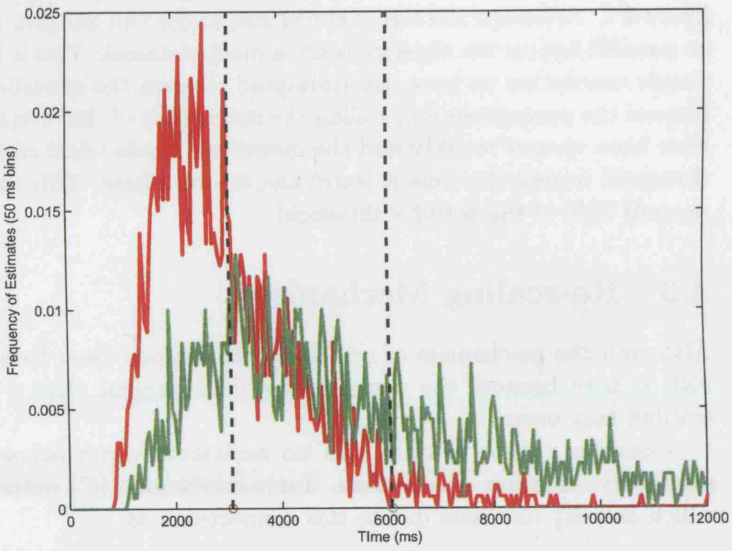

Figure 4.5: Frequency distribution of time estimates made with a learnt threshold. The mean estimates for each distribution (marked with dotted lines) are 3057 ms and 6058 taken over 1800 trials. The targets are 3000 ms and 6000 ms. Training occurred for 200 example trials for each interval.

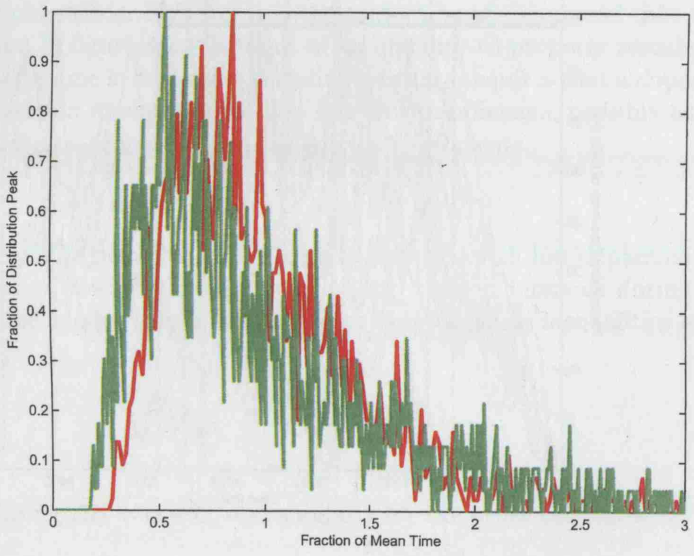

Figure 4.6: The data from figure 4.5 is shown here in mean-invariant coordinates.

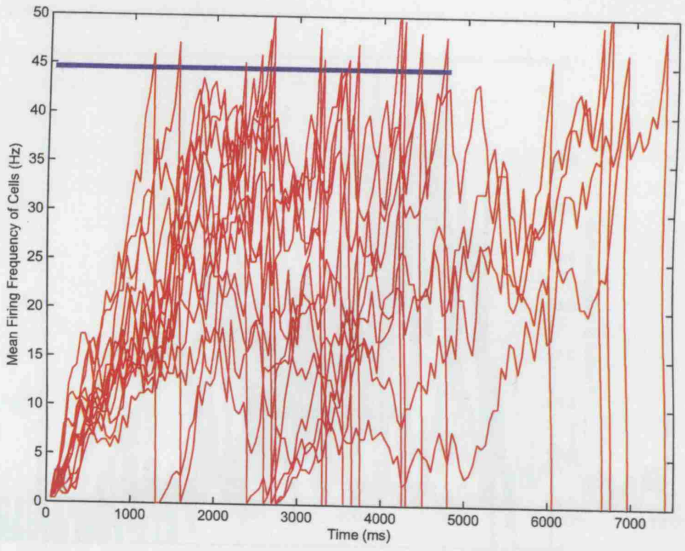

Figure 4.7: A random selection of 1 % of the sustained activity traces used to build up the distributions seen in figures 4.5 and 4.6. The threshold is denoted by the blue line. Estimates are made when the activity crosses the threshold.

The simplest function of T which can rescale activity is linear. However the data from Parkinson's patients shown in figure 4.2 suggests a more complex quadratic dependency may be more appropriate. As such we parameterise $I(T)$ with three co-efficients.

$$I(T) = \alpha + \beta T + \gamma T^2 \tag{4.7}$$

$$(M - \alpha)T_1 + \beta T_1^2 + \gamma T_1^3 = (M - \alpha)T_2 + \beta T_2^2 + \gamma T_2^3$$

If $\gamma = 0$ then it is clear that under normal conditions the linear relationship would suffice. However it is the contention of this model that the error data seen in figure 4.2 is a result of an inability to properly rescale activity when dopamine is depleted. Modeling this data requires that a dopamine depleted version of equation 4.7 has different co-efficients, possibly as a result of a failure to properly learn the correct co-efficients.

$$I'(T) = \alpha' + \beta' T + \gamma' T^2 \tag{4.8}$$

One of the principal effects seen in patients with low dopamine levels is a migration toward the mid point of two trained intervals during testing. Under the model this is equivalent to the following inequalities assuming $T_1 < T_2$.

$$m'(T_1) < m(T_1)$$

$$m'(T_2) > m(T_2)$$

Defining $\Delta\alpha = \alpha - \alpha'$ and similarly for the other two variables $\Delta\beta$ and $\Delta\gamma$.

$$\Delta\alpha + \Delta\beta T_1 + \Delta\gamma T_1^2 > 0$$

$$\Delta\alpha + \Delta\beta T_2 + \Delta\gamma T_2^2 < 0$$

If $\Delta\alpha = 0$ then $\Delta\gamma < 0$. This holds because one of the roots of the quadratic must lie between T_1 and T_2. The condition on $\Delta\beta$ is as follows.

$$T_2 > -\frac{\Delta\beta}{\Delta\gamma} > T_1$$

Written in the original variables this becomes clearer.

$$T_2 > \frac{\beta - \beta'}{\gamma' - \gamma} > T_1$$

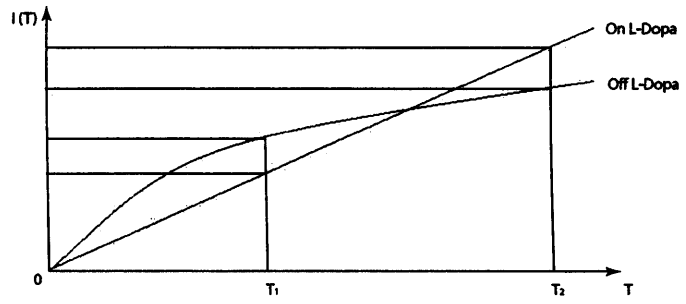

Figure 4.8: Plot shows level of tonic inhibition for subjects both on and off L-Dopa. A linear relationship between Inhibition and presented time interval is assumed in the case of L-Dopa application.

The effect of such a change can be seen in figure 4.8. A linear relationship is used in the 'On L-dopa' case though the essential result is the same if a quadratic is used.

If re-scaling is to work the subject must be able to rapidly determinate when a standard interval has lengthened or shortened. Although the system presented in this model is noisy it is easy to differentiate a time period which is different from that repeated in a previous block of trials. This is because the noisy estimates regress to the mean estimate.

In the event that an unexpectedly short interval is presented the total number of spikes emitted by the cells on that trial will is highly likely to be significantly less than the mean over previous trials. Similarly the total number of spikes emitted when the period presented is unusually long will be significantly greater than the mean. See figure 4.9

4.4 Modeling Responses of Dopamine Depleted Patients

In Malapani's experiment time production training occurred in the first experimental session the day before the testing session. Half of the patients were trained on the short (6 second) interval first; half were trained with the long interval (17 second) interval first. Subjects sat in front of a screen. For each interval training consisted of 10 trials in which the interval was presented by means of a blue square which turned magenta at the end of the interval. There then followed 10 trials in which the blue square did not turn magenta and the subjects were required to mark the end of the interval by releasing the space bar on the keyboard in front of them. In the interval between trials subjects received feedback on their performance via a relative time histogram presented on the screen.

After this pre-training the subjects undertook an encoding session with each of the presented intervals consisting of 20 fixed-interval trials, 30 estimated-interval trials and 10 estimated-interval trials without feedback. The following day subjects faced a decoding session of another 60 trials in which feedback was withheld. Testing order was counterbalanced throughout.

In the model of this data, training or encoding sessions are differentiated from testing or decoding sessions by a single factor. Only in encoding sessions can the readout threshold be learnt. During these trials feedback is provided giving information which can be used to modify the readout connections. If correct (linear) re-scaling fails to occur the threshold can be significantly different for each presented interval. A diagram of this scheme

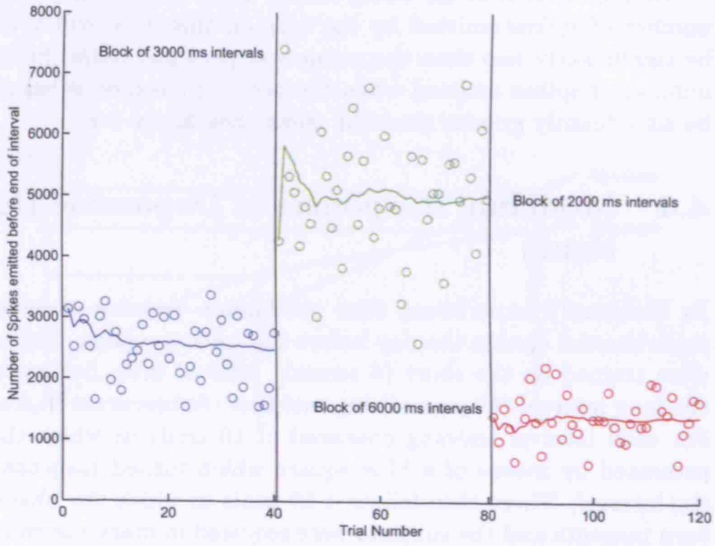

Figure 4.9: This sequential plot of trials shows how the point at which re-scaling is required can be detected. A longer or shorter interval appears as an outlier from the distribution of proceeding intervals. The discriminating variable is the total number of emitted spikes.

can be seen in figure 4.10

A single readout is necessary to avoid the behavioural confusion of multiple readouts with different thresholds. Indeed one of the advantages of this model is that its single readout provides a clear and unambiguous behavioural signal.

In the eventuality that re-scaling does not occur in a linear fashion the readout learns multiple thresholds. In this case the threshold for the training session is the mean of the two thresholds learnt. This is not unreasonable because simple learning mechanisms will tend to drive the connections between pyramidal cells and the readout to take values between the stable points corresponding to each individual threshold.

This explanation for the timing differences seen in L-Dopa depleted patients posits that an impairment in the re-scaling mechanism drives the pattern of behaviour seen in Malapani's experiment. Because re-scaling can be seen as a method of comparing time intervals this theory suggests that L-Dopa depleted patients suffer from a degraded ability to accurately compare intervals - rather than to time per se.

4.5 Discussion

In this final chapter a model of human interval timing has been introduced which uses discrimination based on sustained working memory activity to derive a behavioural signal. The advantages of this model lie in the means by which it uses a defined neural process to generate and draw information from timing processes. Its scope is similar to that of Scalar Expectancy Theory. In addition it predicts a source for the multiplicative noise seen in psychophysical timing data. The adaptability of scalar timing is used to the full by defining a single read-out mechanism which can drive behaviour in an environment where the length of the measured interval varies rapidly in the course of very few trials.

We have also looked at the degree to which ramping activity seen in PFC cells during working memory tasks can be used as part of the internal timing mechanism. The behaviour exhibited by these cells is complex and we have sought to show how this complexity could expand the flexibility of an internal timer. This complexity stems from two principal sources, the fact that cells' dynamic patterns fall into two categories roughly: ramping-up and ramping-down; and the observation that many ramping-up cells scale their activity over the to-be-timed interval.

Ramping down cells are naturally limited. The period over which they

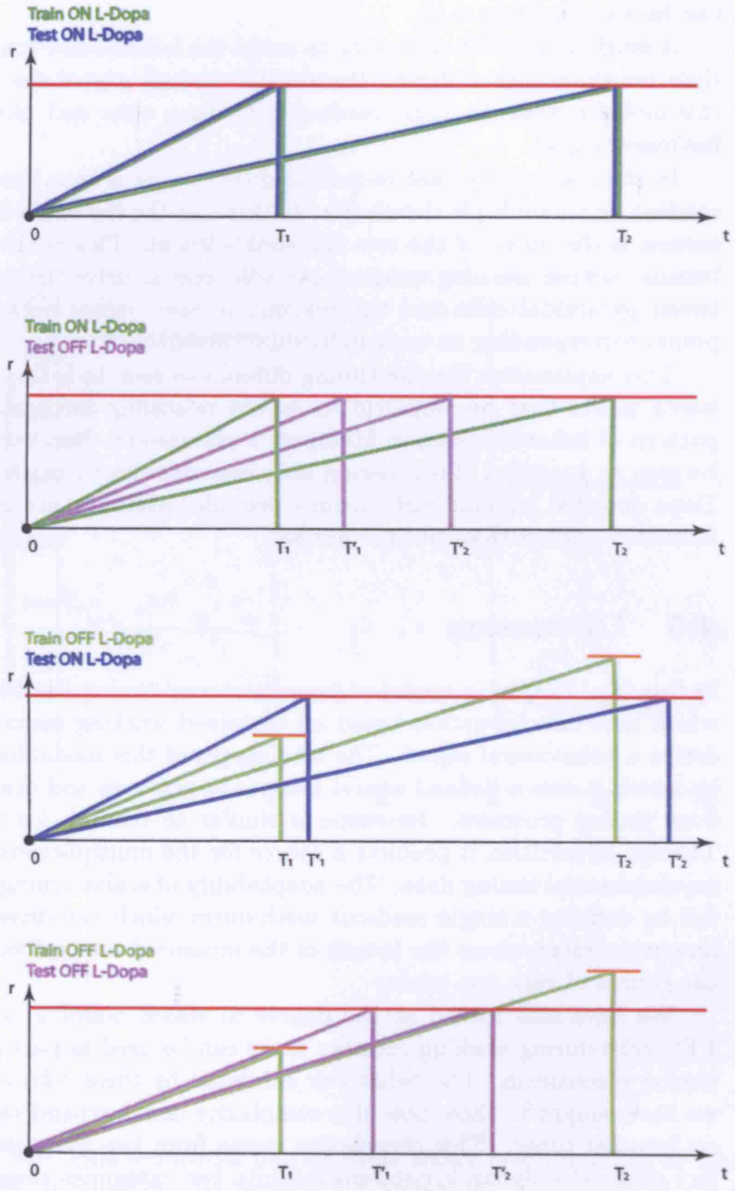

Figure 4.10: Four plots of cellular activity corresponding to each of the four conditions tested by Malapani. Note that a single threshold exists in the testing session. Multiple thresholds can be used in training because the model is able to learn new thresholds in at this stage. This accounts for the quality of the performance in all cases when Training either on or off L-Dopa.

can provide the sole record of the passage time is the period over which their activity decays. When their activity hits a base, the tonic level of firing, all that can be said of the interval elapsed is that it exceeds the lifetime of the sustained activity.

On first inspection this limit problem does not seem to arise for ramping-up cells. The longer the to-be-timed interval the greater the cell activity level at the termination of the interval. However this is physiologically implausible. Cells are limited in the rate at which they may fire by refractory periods and limits on reasonable energy consumption. In practice both sets of cell behaviour are limited.

Once these constraints are recognised it is easy to see that re-scaling of the activity profile to fit experience of the to-be-timed duration offers a way to expand the range of timeable intervals. Under this interpretation re-scaling cells do not measure absolute time but relative time. Cells which re-scale will, on average, reach the same level of activity at the half way point (or the end) of any interval. This makes them a great cue for task such as the peak procedure experiment in which subjects reach the same level of pecking activity half way through the interval before food delivery regardless of the length of the interval. They are also a reasonable cue in the interval timing task where a learnt. interval is reproduced for a block of trials

However tasks which require a knowledge of the absolute passage of time require something extra. In the timeleft and leave-time experiments, subjects are required to make a comparison between intervals. They must also have a signal which gives information about the time elapsed at any point after the start of the interval.

To do these tasks it is necessary to have some kind of internal standard period. This need not be the same interval as the comparison interval in the time-left task or the period of reinforcement in the leave time experiment. Rather what is important is that this interval is invariant so that it the interval experienced can be compared with remembered intervals.

Re-scaling cells cannot signal such an invariant interval since they adjust their activity to the period being timed. However non re-scaling cells are perfect for this purpose. If non re-scaling cell activities form a representation of absolute time, while their re-scaling cousins form a representation of relative time, then the two may be used in conjunction to time periods of arbitrary length without breaking the limits imposed by read-out mechanisms and cell physiology.

Consider a population of non re-scaling cells which ramp down and a population of re-scaling cells which ramp up. On average over many trials

the activity of the non re-scaling cells will be come indistinguishable from their tonic activity level over a standard interval. This may be well before the end of the to-be-timed interval. A measure of the activity level in the population of ramping-up cells at this point would allow the relative interval measured by these cells to be converted to an absolute basis. If the activity of the re-scaling cells is measured at the end of the interval the two measures may be combined to give the absolute interval length.

This thesis therefore contends that re-scaling cells are pivotal in production of an interval clock signal. It makes little sense to suggest that re-scaling cells may be used for one set of timing tasks and non re-scaling cells for another because if one set of cells where used isolation the timer would be rendered quite inflexible.

This thesis does not attempt to explain memory of time intervals. However the theory proposed does require the timer to interact with a short term memory for intervals. It requires ability to record the activities of populations of prefrontal cells and store this information in the short term. It is suggested that re-scaling is achieved by feeding back this information to the re-scaling timer in the form of a tonic inhibitory signal which is linearly related to the activity observed on previous intervals.

The model is obviously somewhat speculative. However it does show that it is possible to learn and reproduce long intervals from neural activity previously only associated with working memory.

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